Synthesis and Structure–Activity Relationships of 6-Heterocyclic-Substituted Purines as Inactivation Modifiers of Cardiac Sodium Channels

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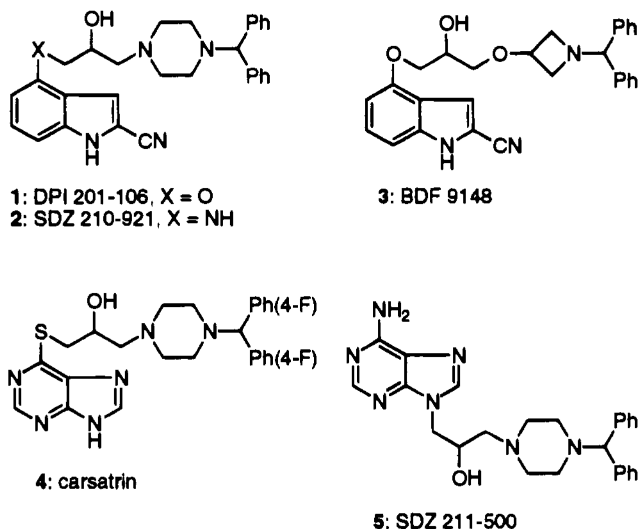
Purine-based analogs of SDZ 211-500 (**5**) were prepared and evaluated as inactivation modifiers of guinea pig or human cardiac sodium (Na) channels expressed in *Xenopus* oocytes. Substances which remove or slow the Na channel inactivation process in cardiac tissue are anticipated to prolong the effective refractory period and increase inotropy and thus have potential utility as antiarrhythmic agents. Heterocyclic substitution at the 6-position of the purine ring resulted in compounds with increased Na activity and potency, with 5-membered heterocycles being optimal. Only minor modifications to the benzhydrylpiperazine side chain were tolerated. Selected compounds which delayed the inactivation of Na channels were found to increase refractoriness and contractility in a rabbit Langendorff heart model, consistent with the cellular mechanism. Activity in both the oocyte and rabbit heart assays was specific to the *S* enantiomers. Preliminary in vivo activity has been demonstrated following intravenous infusion. The most promising compound on the basis of in vitro data is the formylpyrrole (*S*)-**74**, which is 25-fold more potent than DPI 201-106 (**1**) in the human heart Na channel assay.

Introduction

Sodium (Na) channels play a role in both impulse propagation and defining action potential wave forms in mammalian myocardial tissue.[1] Delayed inactivation of Na channels during the action potential plateau has been reported to prolong action potential duration (APD),[2] a property characteristic of class III antiarrhythmic activity.[3] One consequence of delayed Na channel inactivation is subsequent elevation of the intracellular calcium concentration via the sodium/calcium exchange mechanism,[4] which in turn leads to an increase in cardiac contractility.[5] Substances which slow or remove the inactivation process of cardiac Na channels would therefore prolong the effective refractory period (ERP) and increase contractility, thereby offering the potential for use as antiarrhythmic therapy in patients with depressed myocardial contractility. As an extension of our long-standing interest in therapies for the treatment of heart failure and life-threatening arrhythmias, we undertook a study of inactivation modifiers of cardiac Na channels to develop an antiarrhythmic agent devoid of cardiac depression.

Several classes of small molecules are known to act by this mechanism. The most prevalent is DPI 210-106 (1),[6] which has undergone extensive preclinical evaluation as an inotrope,[7] an antiarrhythmic,[8] and a vasodilator[9] and has been evaluated in humans for the treatment of congestive heart failure.[10] Other structurally related compounds which have been shown to delay the inactivation of cardiac Na channels include the cyanoindoles SDZ 210-921 (**2**)[11] and BDF 9148 (**3**),[12] as well as a series of 6-thiopurines exemplified by carsatrin (**4**)[13] and the adenine-based SDZ 211-500 (**5**).[14] We were



intrigued by the diversity of heterocyclic moieties to which the common (hydroxypropyl)benzhydrylpiperazine chain was attached and sought to explore the specific structural requirements within the series **1**–**5**. At the same time, we hoped to probe the roles of the benzhydrylpiperazine (BHP) unit and connecting chain, with the goal of optimizing the activity at the Na channel site while minimizing potential ancillary receptor interactions anticipated by the presence of two pharmacologically prolific fragments.[15]

Chemistry

The coupling of the purine nucleus with the benzhydrylpiperazine side chain was accomplished using two different synthetic routes (Schemes 1 and 2). Initially, targets were prepared according to the method of Ott,[16] wherein the substituted purine **6** was reacted with the benzhydrylpiperazine epoxide **7**[16] in the presence of

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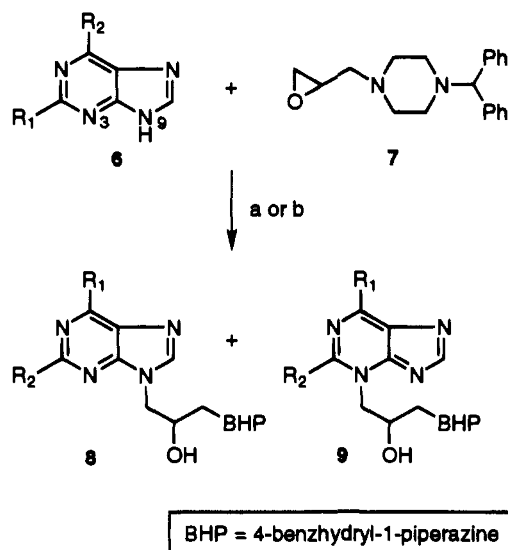
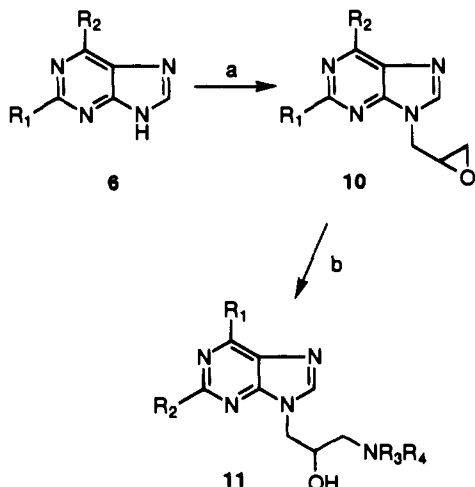
Scheme 1[a]



[a] (a) Method A, 1 N NaOH, dioxane, reflux; (b) method B, DMSO, 120–150 °C.

Scheme 2[a]



[a] Method C: (a) glycidol, triphenylphosphine, DEAD, THF; (b) NHR_3R_4, EtOH, reflux.

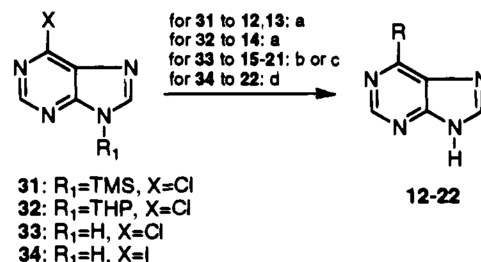
aqueous NaOH to afford a mixture of products alkylated at the N9 (**8**) and N3 (**9**) positions of the purine (method A, Scheme 1). These regiochemical assignments were based on ultraviolet absorption data and supported by HMQC and HMBC high-field NMR experiments. The ratio of **8** to **9** formed under the conditions of method A ranged from 15 to >25:1, as determined by NMR integration of the crude reaction mixture. In general, the relative amount of N3 isomer present in the product mixture was increased modestly by heating the reactants together in DMSO without added base (Scheme 1, method B). Alternatively, purine **6** was reacted with glycidol under Mitsunobu[17] conditions to afford the intermediate epoxide **10** (Scheme 2), which was subsequently reacted with amines in refluxing ethanol (method C). Each of these sequences was employed to prepare enantiomerically enriched products by using (*S*)- or (*R*)-**7**[18] or -glycidol,[19] respectively. Although methods A and B afforded the desired compounds with greater optical purity than method C (>95% ee vs ~80% ee, corresponding to the purity of the epoxide used), the latter gave consistently higher overall yields for the N9 isomers. Thus method C was used when limited quantities of reactants were available. Method B was employed when the N3 isomers were of particular interest.

Table 1. Physical Properties of 6-Heterocyclic-Substituted Purines

compd	R	method	yield, %[a]
12[b]	C_6H_5	D	75
13	2-naphthalenyl	D	32
14[c]	2-thienyl	D	46
15	1-imidazolyl	E	90
16	2-CH_3-1-imidazolyl	*d*	84
17	4-CH_3-1-imidazolyl	E	86
18	1-pyrazolyl	E	100
19	3-CH_3-1-pyrazolyl	E	84
20	4-CH_3-1-pyrazolyl	E	86
21	1-(1,2,4-triazolyl)	E	86
22[e]	$C{\equiv}C_6H_5$	*e*	35
23	1-pyrryl	F	34
24[f]	2,5-$(CH_3)_2$-1-pyrryl	F	24
25	2-CH_3-4,5,6,7-tetrahydroindol-1-yl	F	26
26	3-CHO-1-pyrryl	F	15
27	2-CN-1-pyrryl	*d*	82
28	2-CHO-1-pyrryl	*d*	80
29	3-(1,2,4-oxadiazolyl)	*d*	15
30	4-pyridinyl	*d*	17

[a] Overall yields for multistep syntheses. [b] See refs 21 and 22. [c] See ref 23. [d] See the Experimental Section. [e] See ref 20. [f] See ref 24.

Scheme 3[a]

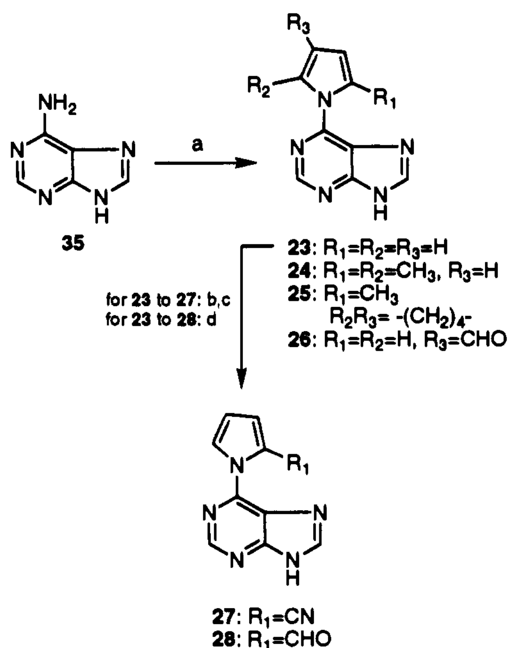


[a] (a) Method D, RMgBr, $NiCl_2(dppp)$ (cat.), Et_2O; (b) method E, excess 1*H*-azole, melt; (c) 1*H*-azole, *n*-butanol, reflux; (d) phenylacetylene, triphenylphosphine (cat.), $Pd(OAc)_2$ (cat.), Et_3N, THF.

The 6-heterocyclic-substituted purine nuclei **12**–**30** (Table 1) were synthesized according to Schemes 3–6. At the time this work was performed, only compounds **12** and **22** were known. Purine **22** was prepared according to the published synthesis, whereby phenylacetylene was coupled with 6-iodopurine (**34**) via a Heck reaction.[20] We had difficulty reproducing either of the reported syntheses of **12**, involving treatment of 6-chloropurine with excess phenyllithium[21] or reaction of 6-(methylthio)purine with Grignard reagents under nickel catalysis.[22] We found that the nickel-catalyzed Grignard coupling of phenylmagnesium bromide and TMS-protected 6-chloropurine (**31**) gave a more reliable method for preparing **12** on a multigram scale (Scheme 3, method D). This procedure was also applied to the syntheses of **13** and **14** using the appropriate Grignard reagents.[23]

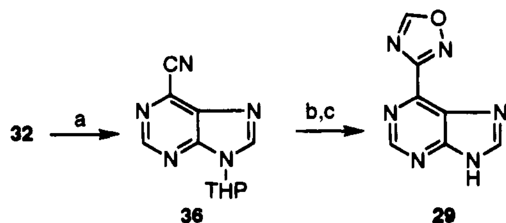
The azole-substituted purines **15-21** were prepared by treating 6-chloropurine with an excess of the appropriate 1*H*-azole at 150 °C (Scheme 3, method E) or

Scheme 4[a]



[a] (a) Method F, HOAc, reflux with the following: for **23**, 2,5-dimethoxytetrahyrofuran, for **24**, 2,5-hexanedione, for **25**, 2-(2-oxopropyl)cyclohexanone,[44] for **26**, 2,5-dimethoxy-3-tetrahyrofuran-carboxaldehye; (b) 3,4-dihyro-2*H*-pyran, *p*-TsOH (cat.), EtOAc; (c) $ClSO_2NCO$, CH_3CN, then DMF; (d) $POCl_3$, DMF.

Scheme 5[a]



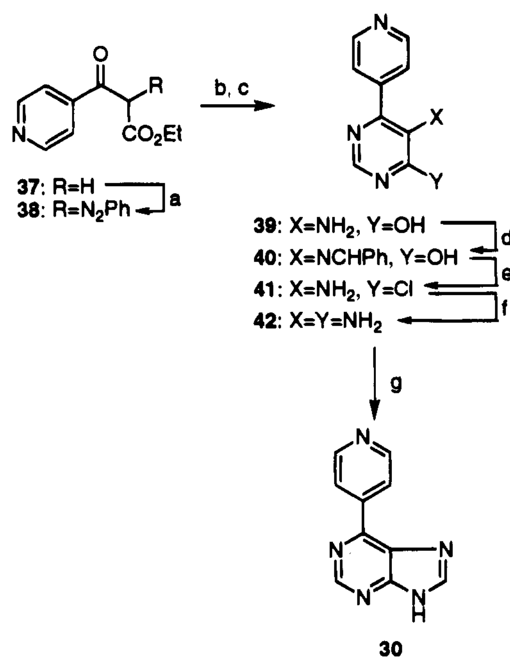
[a] (a) KCN, DMSO; (b) $H_2NOH{\cdot}HCl$, KOH, EtOH, reflux; (c) $HC(OEt)_3$, *p*-TsOH (cat.), reflux.

with 3 equiv of 1*H*-azole in *n*-butanol at reflux. The pyrrole derivatives **23**-**26** were synthesized from adenine (**35**) and the requisite 1,4-dicarbonyl or equivalent in hot acetic acid (Scheme 4, method F). In the case of the dimethylpyrrole **24**, it was necessary to remove water from the reaction vessel via continuous azeotropic distillation to drive the equilibrium to the desired product.[24] The pyrrole ring of **23** is reactive to electrophiles, allowing for the introduction of a nitrile group at the 2-position (**27**) using phenylsulfonyl isocyanate and DMF[25] after THP protection of the purine. Similarly, treatment of **23** with phosphorus oxychloride in DMF afforded the aldehyde **28**.

The oxadiazole **29** was prepared according to Scheme 5. The THP-protected 6-chloropurine (**32**)[13] was reacted with KCN in DMSO to afford the protected 6-cyanopurine **36**. Subsequent treatment of **36** with hydroxylamine in ethanol followed by acid-catalyzed cyclization of the intermediate amidoxime with triethyl orthoformate gave **29**.

Attempts to synthesize the 4-pyridinylpurine **30** via the nickel-catalyzed Grignard coupling according to Scheme 3 were not successful. An alternative synthesis was performed in which the purine ring was constructed using a modification of the method described by Giner-Sorolla and Bendich[26] (Scheme 6). *β*-Keto ester **37**[27] was

Scheme 6[a]



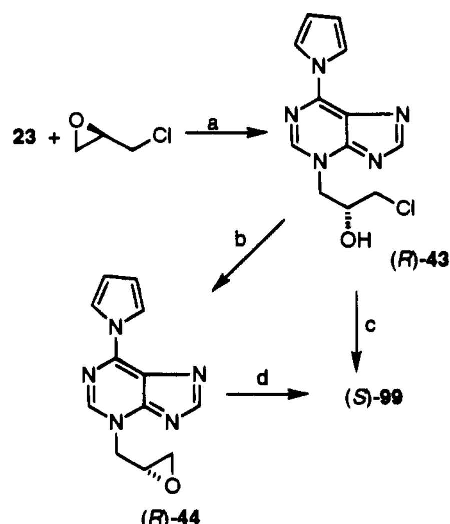
[a] (a) ClN_2Ph, NaOAc, EtOH, water; (b) thiourea, NaOEt, EtOH; (c) Raney nickel, NH_4OH; (d) PhCHO, 3 Å sieves, 150 °C; (e) $POCl_3$, reflux, then 2 N HCl; (f) NH_4OH, EtOH, 150 °C; (g) H_2NCHO, 150 °C.

treated with benzenediazonium chloride to give the phenylazo derivative **38**. Pyrimidone formation with thiourea followed by Raney nickel reduction in ammonium hydroxide afforded the aminopyrimidone **39**. The amino group was protected as the *N*-benzilidineamine **40**, and treatment with phosphorus oxychloride gave the chloropyrimidine **41**. Aminolysis with ammonium hydroxide in ethanol at 150 °C followed by ring closure with formamide at 150 °C afforded compound **30**.

As the structure–activity relationship (SAR) development of the target series progressed and Na channel inactivation was found to be specific for the *S* enantiomers, the synthesis of racemic targets was discontinued. Methods A–C were subsequently performed with enantiomerically enriched epoxides (*S*)-**7**[18] or (*S*)-glycidol,[19] as described above. It also became desirable to develop an alternative to methods A or B for preparing the minor, N3-alkylated products selectively and in reasonable yield. Thus, a regioselective synthesis of (*S*)-**99** was devised (Scheme 7), based on the reported N3-alkylation of adenine with epichlorohydrin under acidic conditions.[28] In an analogous fashion, the pyrrolylpurine **23** was treated with (*R*)-epichlorohydrin in hot acetic acid to give exclusively the N3 chlorohydrin (*R*)-**43**. Upon workup with aqueous NaOH, (*R*)-**43** spontaneously cyclized to the epoxide (*R*)-**44**, and subsequent treatment with BHP in hot ethanol gave the desired product (*S*)-**99**. Alternatively, chlorohydrin (*R*)-**43** was converted to (*S*)-**99** in a single step using BHP and sodium hydride in hot DMSO. The product (*S*)-**99** obtained using either of these procedures was identical in all respects to that prepared from **23** and (*S*)-**7** using method A (Scheme 1). Unfortunately, attempts to extend this method to other N3 regioisomers such as (*S*)-**100** were not successful.

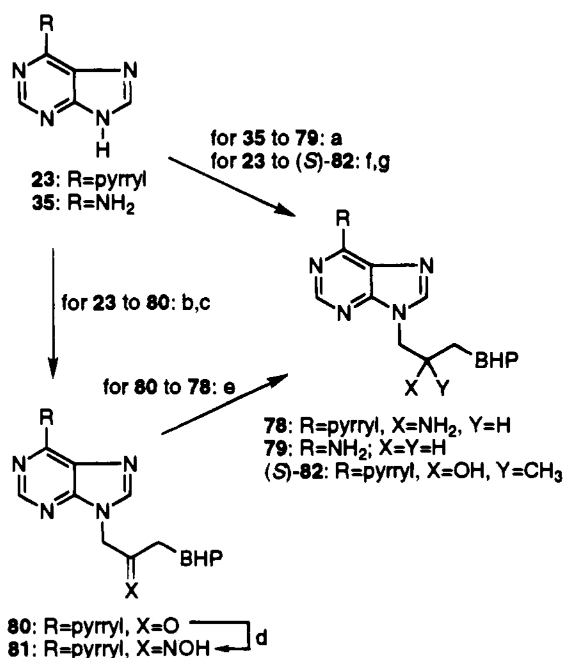
Modification of the hydroxyl functionality on the aliphatic chain was also investigated (Scheme 8). The deshydroxy analog of **5** (**79**) was prepared by alkylating

Scheme 7[a]



[a] (a) HOAc, reflux; (b) NaOH/water; (c) NaH, BHP, DMSO; (d) BHP, EtOH.

Scheme 8[a]



[a] (a) K_2CO_3, DMF, 1-(3-chloropropyl)benzhydrylpiperazine;[29] (b) 7, method A; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (d) $NH_2OH{\cdot}HCl$, NaOH, EtOH/water; (e) NH_4OH, $NaBH_3CN$, CH_2Cl_2, CH_3OH; (f) (*R*)-2-methylglycidol, DEAD, triphenylphosphine, THF; (g) BHP, EtOH.

adenine (**35**) with 1-(3-chloropropyl)benzhydrylpiperazine.[29] Swern oxidation[30] of **56** gave the ketone **80**, which was converted to the oxime **81** under standard conditions. The reductive amination of **80** with ammonium acetate and sodium cyanoborohydride[31] afforded the primary amine **78**. The methyl-substituted compound (*S*)-**82** was prepared from the Mitsunobu coupling of **23** with (*R*)-2-methylglycidol followed by epoxide opening with benzhydrylpiperazine as in method C.

Structure–Activity Relationships

The effect of test compounds on the inactivation processes of cardiac Na channels was assessed using voltage clamp techniques to monitor sodium currents

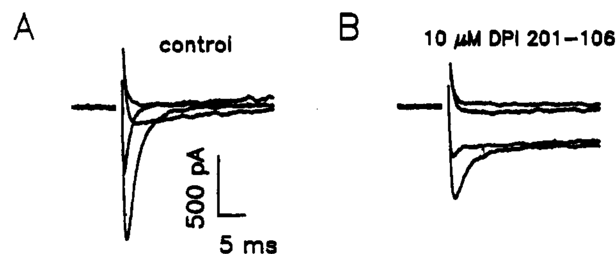
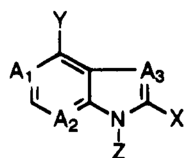


Figure 1. Effects of DPI 201-106 on human heart Na currents.[32] (A) Control current records elicited by test depolarizations from −100 to −60, −40, −20, and 0 mV. (B) Currents elicited by applying the same test depolarizations used for panel A following a 10 min exposure to 10 μM DPI 201-106.

through heart channels expressed in *Xenopus* oocytes. In general, oocytes were injected with cRNA, and after an incubation period of 1−3 days, electrophysiological recording was performed using a two-microelectrode voltage clamp.[32] Current amplitudes were measured during a series of stepwise depolarizations from −100 to −10 mV, and drug-treated current records were compared with controls. To illustrate, representative human heart current records are shown in Figure 1,[32] before (A) or after (B) exposure to 10 μM DPI 201-106 (**1**). The inward current remaining at the end of the pulse (Figure 1B) is indicative of the slowing or removal of inactivation of the Na channels by the test agent. These effects on channel inactivation (i.e., intrinsic activity) were quantified by calculating the percent change in total current integral for drug-treated oocytes vs control, with active compounds generally exhibiting increases in current integral of >100%. It is important to recognize that the shape of the current traces is perhaps more indicative of activity than the measured integral values, although these visual effects are difficult to quantify. Complications arise when delayed inactivation, which results in increased current integrals, is accompanied by current block, which reduces these integrals. Therefore, while the percent increase in current integral is a good indication of activity vs inactivity, this number alone was judged insufficient to rank-order the potencies of test agents. To that end, the relative potencies of active compounds were estimated by calculating the effective concentration that produced a 50% increase in current integral over control values (EC_{50}). The EC_{50} value reflects potency at a concentration slightly above the activity threshold, which was an important consideration for this class of compounds. At higher concentrations, these compounds often began to block Na currents, which resulted in diminished current integrals and biphasic concentration−response curves. By focusing on the lower concentration range, complications resulting from current block could be minimized. Current integrals were measured at three or more concentrations for each compound ($n \geq 3$/concentration), and this entire data set was pooled to generate a single EC_{50} value.

During the course of this research, the oocyte assay for Na channel inactivation underwent a significant modification. While the activity of target compounds was initially measured on guinea pig heart channels expressed in *Xenopus* oocytes,[33] the subsequent cloning and expression of human heart Na channel cDNA in *Xenopus* oocytes[34] led to the exclusive use of the human system as the preferred primary assay for inactivation

Table 2. Effect of Heterocyclic Nucleus Modification on the Inactivation of Sodium Channels Expressed in *Xenopus* Oocytes



compd	Y	A_1	A_2	A_3	X	Z	gp oocyte,[a] % change
1	OR[b]	CH	CH	CH	CN	H	239 ± 97
4	SR	N	N	N	H	H	*c*
5	NH_2	N	N	N	H	R	212 ± 37
45	OR	CH	CH	CH	H	H	−29 ± 5
46	H	N	N	N	H	R	288 ± 62
47	H	CH	N	N	H	R	154 ± 24
48	H	CH	CH	N	H	R	42 ± 19
49	H	CH	CH	CH	H	R	36 ± 3
50	H	CH	N	CH	H	R	−71 ± 17

[a] In vitro assay of inactivation modification obtained from current records of guinea pig heart Na channels expressed in *Xenopus* oocytes. Percent change (± SEM) was determined by measuring the increase in current integral in the presence of test agent vs control at 10 μM. See the Experimental Section for detail. [b] R = $CH_2CHOHCH_2BHP$; BHP = 4-benzhydryl-1-piperazine. [c] Not determined in the guinea pig oocyte, although activity in the human heart oocyte assay is comparable to that of **1**.

activity.[32] Due to the limited number of compounds evaluated in both assays, the nature of the correlation between these two species is unclear. However, while the degree of Na channel activity differs between the assays, the rank-order potencies are consistent among the compounds examined.

Effects on the cardiac ERP were determined using a rabbit Langendorff heart model, for which EC_{20} values correspond to the concentration of test agent that produced a 20 ms increase in ERP (see the Experimental Section). Inotropic effects were assessed by measuring d*P*/d*t* and are expressed as the concentration which increases contractility by 20%. The oocyte and Langendorff data are summarized in Tables 2−6.

Preliminary in vitro assessment of the known sodium channel inactivation modifiers **1**−**5** indicated that there was some flexibility with respect to the heterocyclic component (2-cyanoindole vs 6-thiopurine vs adenine) to which the common 2-hydroxypropyl-3-benzhydrylamine side chain was attached. The structural requirements for this heterocyclic nucleus were probed with the compounds listed in Table 2. When the cyano group of **1** was replaced by hydrogen (**45**[35]), all Na channel activity was lost. In the purine series, the adenine **5** and its desamino analog **46** were equipotent in vitro at the screening concentration of 10 μM, increasing the Na current integral by >200% over controls. The azabenzimidazole **47** had somewhat diminished activity, while the benzimidazole **48**, indole **49**, and azaindole **50** were inactive. On the basis of these initial observations, purines **5** and **46** were used as lead structures for the design and synthesis of new analogs.

The effect of substitution on the purine ring is summarized in Table 3. When the amino group of **5** was replaced with small, acyclic substituents such as H (**46**) or Cl (**51**), the in vitro activity was at least equivalent to that of DPI (**1**). The 6-methyl purine analog (*S*)-**52** was 1.5-fold less potent than **1**, while the cyano derivative **53** showed a 4-fold increase in potency as indicated by the oocyte EC_{50}. Analogs of **5** in which the purine 6-amino group is substituted with benzyl (**54**) or incorporated into a piperidine ring (**55**) were devoid of activity. However, incorporation of the 6-amino group into a heterocyclic ring led to an increase in activity. The pyrrole (**56**) and imidazole (**57**) derivatives each showed a 3-fold increase in potency compared to **5**, while the pyrazole (**58**) and 1,2,4-triazole (**59**) analogs were 9-fold more potent in vitro. The activity of the related oxadiazole derivative (*S*)-**60** was substantially reduced; however, the 2-thienyl analog (*S*)-**61** was similar in potency to **57**, more readily seen by the data presented in Table 6.[36] Two compounds with 6-membered heterocycles at the purine 6-position were prepared; the phenyl (**62**) and 4-pyridinyl [(*S*)-**63**] analogs had potencies similar to **5**. The 2-naphthyl [(*S*)-**64**], benzyl (**65**), and phenylethynyl (**66**) derivatives showed no Na channel activity.

The effect of substitution on the pyrrole, imidazole, and pyrazole rings of **56**−**58** was also explored. The 2-methylimidazole **67** retained in vitro potency, while the 4-methylimidazole analog **68** was at least 5-fold less potent than the unsubstituted imidazole **57**. In the case of the pyrazoles, the 3-methyl derivative **69** retained very little in vitro activity and the 4-methylpyrazole **70** was 3-fold less potent than **58**. There was no Na channel activity resident in the 2,5-dimethylpyrrole **71** nor in the tetrahydroindole derivative **72**. However, substitution at the 2-position of the pyrrole ring with CN [(*S*)-**73**] and CHO [(*S*)-**74**] gave increases in potency of 5- and 25-fold, respectively, compared to **1**. Compound (*S*)-**75**, the 3-formyl derivative of (*S*)-**56**, was essentially devoid of activity. While the 6-position of the purine ring was tolerant of substitution, the analogs possessing a trifluoromethyl group [(*S*)-**76**] or a 4-pyridinyl group (**77**) at the purine 2-position were inactive at the screening concentration of 10 μM.

Several modifications were made to the hydroxyl on the propyl side chain of compounds **5** and **56** (Table 4). Replacement of the hydroxyl of **56** with amino gave **78**, which was of comparable potency to **56**. Compound **79**, the deshydroxy analog of **5**, was devoid of in vitro activity, as were the ketone (**80**) and oxime (**81**) derivatives. Addition of a methyl group to the hydroxyl-bearing carbon of **56** [(*S*)-**82**] also resulted in a loss of activity.

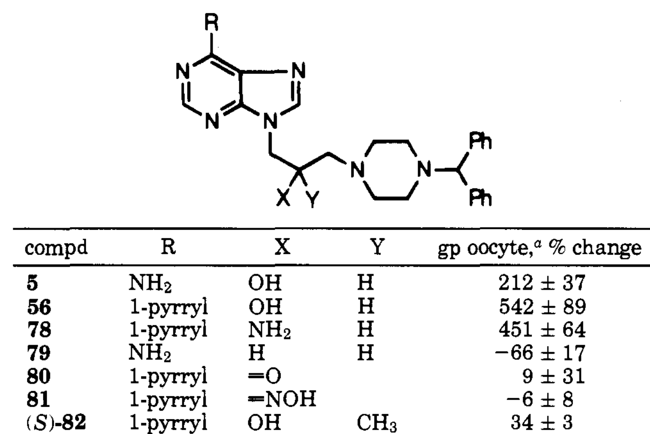
Using the pyrrolylpurine **56** as the framework for comparison, modifications were made to both the benzhydryl and piperazine moieties (Table 5). The fluorinated benzhydryl derivative **83** was of comparable potency to **56**; the corresponding chloro analog **84** could not be tested due to insolubility. Removal of one of the benzhydryl phenyl rings (**85**) resulted in a 4-fold decrease in activity; removal of both phenyl rings gave the 4-methylpiperazine **86**, which was devoid of in vitro activity. Other modifications to the benzhydryl moiety of **56** also abolished activity. These included piperazines substituted at the 4-position with 2,2-diphenylethyl (**87**), 1-phenylethyl (**88**), and diphenylacetonyl (**89**). Two compounds were prepared in which the benzhydryl phenyl rings were conformationally restrained; the 9-fluorenyl derivative **90** was inactive, while the 5-dibenzosuberyl analog **91** retained modest Na channel activity. Replacement of one of the phenyl groups of **56** with 4-pyridinyl or *o*-tolyl gave compounds **92** and **93**, respectively; both showed somewhat diminished activity compared to **56**. The role of the piperazine ring of

Table 3. Inactivation Effects of Substituted Purines on Sodium Channels Expressed in *Xenopus* Oocytes

compd	R1	R2	gp oocyte[a] % change	gp oocyte[a] EC_{50}	HH1 oocyte[a] % change	HH1 oocyte[a] EC_{50}	rabbit Langendorff[b] ERP EC_{20}	rabbit Langendorff[b] d*P*/d*t*
1			239 ± 97	1920	174 ± 47	2310	430 ± 220	NE[c]
5	H	NH_2	212 ± 37	1410	*d*	*d*	307 ± 64[e]	128 ± 12
46	H	H	288 ± 62	796	*d*	*d*	95 ± 14	110 ± 39
51	H	Cl	*d*	*d*	176 ± 23	1950	*d*	*d*
(*S*)-**52**	H	CH_3	*d*	*d*	105 ± 6	3990	*d*	*d*
53	H	CN	1328 ± 900	399	*d*	*d*	260 ± 50[e]	250 ± 60
54	H	$NHCH_2Ph$	−77 ± 10	*d*	*d*	*d*	*d*	*d*
55	H	piperidinyl	26 ± 35	*d*	*d*	*d*	*d*	*d*
56	H	1-pyrryl	542 ± 89	580	*d*	*d*	*d*	*d*
57	H	1-imidazolyl	680 ± 231	630	*d*	*d*	27 ± 10	46 ± 8
58	H	1-pyrazolyl	372 ± 33	158	*d*	*d*	81 ± 40	40 ± 10
59	H	1-(1,2,4-triazolyl)	1664 ± 409	204	*d*	*d*	57 ± 18[e]	60 ± 12
(*S*)-**60**	H	3-(1,2,4-oxadiazolyl)	*d*	*d*	138 ± 14	*d*	*d*	*d*
(*S*)-**61**	H	2-thienyl	*d*	*d*	116 ± 12	1030	*d*	*d*
62	H	C_6H_5	151 ± 12	1260	*d*	*d*	*d*	*d*
(*S*)-**63**	H	4-pyridinyl	*d*	*d*	99 ± 30	2800	*d*	*d*
(*S*)-**64**	H	2-naphthyl	−66 ± 20	*d*	*d*	*d*	*d*	*d*
65	H	$CH_2C_6H_5$	−100 ± 0	*d*	*d*	*d*	*d*	*d*
66	H	$C{\equiv}C\text{-}C_6H_5$	9 ± 8	*d*	*d*	*d*	*d*	*d*
67	H	$2\text{-}CH_3$-1-imidazolyl	*d*	*d*	158 ± 19	1260	90 ± 30[e]	60 ± 30
68	H	$4\text{-}CH_3$-1-imidazolyl	126 ± 112	>3000	*d*	*d*	NE	*d*
69	H	$3\text{-}CH_3$-1-pyrazolyl	*d*	*d*	40 ± 19	*d*	*d*	*d*
70	H	$4\text{-}CH_3$-1-pyrazolyl	868 ± 36	585	*d*	*d*	216 ± 118	300 ± 157
71	H	$2,5\text{-}(CH_3)_2$-1-pyrryl	−47 ± 26	*d*	*d*	*d*	*d*	*d*
72	H	$2\text{-}CH_3$-4,5,6,7-tetrahydroindol-1-yl	8 ± 14	*d*	*d*	*d*	*d*	*d*
(*S*)-**73**	H	2-CN-1-pyrryl	*d*	*d*	456 ± 66	447	57 ± 24	22 ± 2
(*S*)-**74**	H	2-CHO-1-pyrryl	*d*	*d*	904 ± 91	78	17 ± 1	17 ± 1
(*S*)-**75**	H	3-CHO-1-pyrryl	*d*	*d*	63 ± 17	7260	*d*	*d*
(*S*)-**76**	CF_3	1-pyrryl	−13 ± 8	*d*	*d*	*d*	*d*	*d*
77	4-pyridinyl	NH_2	−2 ± 11	*d*	*d*	*d*	*d*	*d*

[a] In vitro assay of inactivation modification obtained from current records of guinea pig heart or human heart Na channels expressed in *Xenopus* oocytes. Percent change (± SEM) was determined by measuring the increase in current integral in the presence of test agent vs control at 10 μM. EC_{50} is the nanomolar concentration of test agent which produced a 50% increase in current integral as extrapolated from a fitted dose−response curve. See the Experimental Section for detail. [b] In vitro assay of antiarrhythmic activity and inotropy (±SEM). ERP EC_{20} is the nanomolar concentration of test agent which prolonged the effective refractory period by 20 ms. d*P*/d*t* is the nanomolar concentration of test agent which increased contractility by 20%. See Experimental Section for detail. [c] NE = no effect at ≤3 μM. [d] Not determined. [e] Spontaneous fibrillation observed at ≤1 μM.

Table 4. Effect of Hydroxyl Modification on the Inactivation of Sodium Channels Expressed in *Xenopus* Oocytes



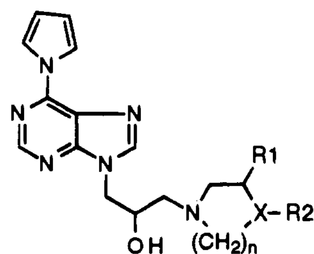
compd	R	X	Y	gp oocyte,[a] % change
5	NH_2	OH	H	212 ± 37
56	1-pyrryl	OH	H	542 ± 89
78	1-pyrryl	NH_2	H	451 ± 64
79	NH_2	H	H	−66 ± 17
80	1-pyrryl	=O		9 ± 31
81	1-pyrryl	=NOH		−6 ± 8
(*S*)-**82**	1-pyrryl	OH	CH_3	34 ± 3

[a] See footnote *a* of Table 2.

compound **56** was also examined. Ring expansion to the homopiperazine **94** resulted in substantial activity loss. The 4-benzhydrylpiperidine **95** retained modest activity, while the hydroxylated piperidine **96** was inactive. The Na channel activity of the (diphenylmethylene)piperidine **97** was modest. Addition of a methyl group onto the piperazine ring of **56** gave **98**, which showed sustained activity as a mixture of diastereomers.

It has been reported that the Na channel inactivation activity of DPI 201-106 (**1**) is enantioselective and resides in the *S* enantiomer.[37] The separate enantiomers of compounds **5** and **56** were examined, and in both cases the *S* enantiomer was more active than the racemic mixture (Table 6). As the *R* isomers of **5** and **56** were devoid of Na channel activity, no additional *R* compounds were prepared. In a few instances, sufficient quantities of the minor N3 regioisomers were isolated from the N9 syntheses, allowing us to explore the relationship of side chain position to activity. The effects of chirality and regiochemistry are summarized in Table 6. While activity differences within the pairs of racemic and *S* compounds varied, in all cases the *S* enantiomers were more potent than the racemates in the guinea pig oocyte assay (e.g., **5**, **56**−**59**, and **62**). A single pair of compounds [**67** and (*S*)-**67**] was evaluated

Table 5. Effect of Benzhydrylpiperazine Modification on the Inactivation of Sodium Channels Expressed in *Xenopus* Oocytes



compd	*n*	X	R1	R2	gp oocyte,[a] % change
56	2	N	H	$CH(C_6H_5)_2$	542 ± 89
83	2	N	H	$CH(4\text{-}F\text{-}C_6H_4)_2$	521 ± 35
84	2	N	H	$CH(4\text{-}Cl\text{-}C_6H_4)_2$	insoluble
85	2	N	H	$CH_2C_6H_5$	182 ± 87
86	2	N	H	CH_3	−35 ± 34
87	2	N	H	$CH_2CH(C_6H_5)_2$	−47 ± 15
88	2	N	H	$CH(CH_3)C_6H_5$	−32 ± 48
89	2	N	H	$COCH(C_6H_5)_2$	6 ± 7
90	2	N	H	9-fluorenyl	−19 ± 27
91	2	N	H	5-dibenzosuberyl	120 ± 31
92	2	N	H	$CH(C_6H_5)$(4-pyridinyl)	326 ± 102
93	2	N	H	$CH(C_6H_5)(2\text{-}CH_3\text{-}C_6H_4)$	209 ± 70
94	3	N	H	$CH(C_6H_5)_2$	38 ± 30
95	2	CH	H	$CH(C_6H_5)_2$	108 ± 19
96	2	CH	H	$COH(C_6H_5)_2$	−10 ± 28
97	2	C=C	H	$(C_6H_5)_2$	94 ± 35
98	2	N	CH_3	$CH(C_6H_5)_2$	839 ± 340

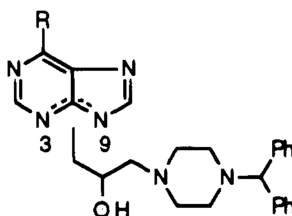
[a] See footnote *a* of Table 2.

in the human heart oocyte assay. While the *S* enantiomer exhibited a dramatic increase in current integral compared to the racemate at 10 μM, the effects were very similar at 3 μM.[38] The resulting EC_{50} calculated from this concentration−response data suggest that the *S* enantiomer has comparable potency to the racemate. In general, the greater maximal effect on current integral of a pure *S* enantiomer compared to the corresponding racemic mixture most likely reflects the blocking of current by the *R* component in the latter, which attenuates the effect of the active component with respect to increases in current integral. While the EC_{50} calculated for (*S*)-**67** suggests that this enantiomer was less potent than the racemate, the data at 3 and 10 μM, in fact, suggest a slightly greater effect for the *S* enantiomer.

The activity differences between several pairs of N9 and N3 regioisomers also varied, but in all cases but one, the N3 analogs were at least as potent as the corresponding N9 isomers in the oocyte assays [cf. (*S*)-**100** and (*S*)-**58**, (*S*)-**103** and (*S*)-**62**, (*S*)-**104** and (*S*)-**63**] if not more potent [cf. (*S*)-**99** and (*S*)-**56**, (*S*)-**102** and (*S*)-**61**]. The exception is the oxadiazolyl pair (*S*)-**101** and (*S*)-**60** in which the N9 isomer showed modest activity while the N3 isomer was inactive.

Examination of selected oocyte-active compounds in the rabbit Langendorff assay revealed qualitatively similar trends to those seen in the oocyte (Tables 3 and 6). Increases in antiarrhythmic and inotropic potency ranging from 3- to 10-fold were observed upon replace-

Table 6. Effect of Chirality and Regiochemistry on the Inactivation of Sodium Channels Expressed in *Xenopus* Oocytes



compd	pt of attach	R	gp oocyte[a]		HH1 oocyte[a]		rabbit Langendorff[b]	
			% change	EC_{50}	% change	EC_{50}	ERP EC_{20}	d*P*/d*t*
(±)-**1**			239 ± 97	1920	174 ± 47	2310	430 ± 220	NE[c]
(±)-**5**	9	NH_2	212 ± 37	1410	*d*	*d*	307 ± 64[e]	128 ± 12
(*S*)-**5**	9	NH_2	139 ± 49	1035	*d*	*d*	109 ± 8[e]	89 ± 13
(*R*)-**5**	9	NH_2	−43 ± 19	*d*	*d*	*d*	5240 ± 970	1140 ± 89
(±)-**56**	9	1-pyrryl	542 ± 89	580	*d*	*d*	*d*	*d*
(*S*)-**56**	9	1-pyrryl	390 ± 85	245	*d*	*d*	332 ± 128	2230 ± 500
(*R*)-**56**	9	1-pyrryl	21 ± 9	*d*	*d*	*d*	NE	*f*
(*S*)-**99**	3	1-pyrryl	711 ± 217	85	540 ± 119	290	43 ± 20	377 ± 240
(±)-**57**	9	1-imidazolyl	680 ± 231	630	*d*	*d*	27 ± 10	46 ± 8
(*S*)-**57**	9	1-imidazolyl	*d*	*d*	459 ± 87	1250	30 ± 10[e]	*d*
(±)-**58**	9	1-pyrazolyl	372 ± 33	158	*d*	*d*	81 ± 40	40 ± 10
(*S*)-**58**	9	1-pyrazolyl	1226 ± 441	99	540 ± 147	900	18 ± 10[e]	40 ± 20
(*S*)-**100**	3	1-pyrazolyl	*d*	*d*	369 ± 16	900	74 ± 5[e]	148 ± 49
(±)-**59**	9	1-(1,2,4-triazolyl)	1664 ± 409	204	*d*	*d*	57 ± 18[e]	60 ± 12
(*S*)-**59**	9	1-(1,2,4-triazolyl)	*d*	*d*	393 ± 50	920	35 ± 16[e]	43 ± 20
(*S*)-**60**	9	3-(1,2,4-oxadiazolyl)	*d*	*d*	140 ± 17	*d*	*d*	*d*
(*S*)-**101**	3	3-(1,2,4-oxadiazolyl)	*d*	*d*	−6 ± 1	*d*	*d*	*d*
(*S*)-**61**	9	2-thienyl	*d*	*d*	116 ± 12	1030	*d*	*d*
(*S*)-**102**	3	2-thienyl	*d*	*d*	437 ± 92	433	*d*	*d*
(±)-**62**	9	C_6H_5	151 ± 12	1260	*d*	*d*	*d*	*d*
(*S*)-**62**	9	C_6H_5	413 ± 166	526	128 ± 13	2000	425 ± 160	NE
(*S*)-**103**	3	C_6H_5	378 ± 83	160	201 ± 7	1600	141 ± 50	434 ± 250
(*S*)-**63**	9	4-pyridinyl	*d*	*d*	99 ± 30	2800	*d*	*d*
(*S*)-**104**	3	4-pyridinyl	*d*	*d*	265 ± 29	2100	*d*	*d*
(±)-**67**	9	2-CH_3-1-imidazolyl	*d*	*d*	158 ± 19	1260	90 ± 30[e]	60 ± 30
(*S*)-**67**	9	2-CH_3-1-imidazolyl	*d*	*d*	1449 ± 541	2700	*d*	*d*

[a−e] See corresponding footnotes of Table 3. [f] Negative inotropic effect observed.

Table 7. Physical Properties of 6-Heterocyclic-Substituted Purines

compd	mp, °C	method	yield, %	formula[a]
46	124–126	A	80	$C_{25}H_{28}N_6O$[b]
47	124–127	[c]	30	$C_{26}H_{29}N_5O$
48	183–185	[c]	51	$C_{27}H_{30}N_4O$
49	58–60	[c]	35	$C_{28}H_{31}N_3O \cdot 0.75H_2O$
50	122–126	[c]	16	$C_{27}H_{30}N_4O$
51	181–183	[c]	61	$C_{25}H_{27}ClN_6O$[b]
(*S*)-**52**	200–203	B	24	$C_{26}H_{30}N_7O \cdot 2HCl \cdot 2H_2O$
53	162–165	C	33	$C_{26}H_{27}N_7O \cdot 2HCl \cdot 1.5H_2O$
54	176–178	A	32	$C_{32}H_{35}N_7O$
55	105–107	A	46	$C_{30}H_{37}N_7O \cdot 0.5H_2O$
56	166–168	A	25	$C_{29}H_{31}N_7O$
(*S*)-**56**	156–158	A	17	$C_{29}H_{31}N_7O$
(*R*)-**56**	156–158	A	25	$C_{29}H_{31}N_7O$
57	178–180	C	50	$C_{28}H_{30}N_8O \cdot 0.25H_2O$
(*S*)-**57**	163–165	[c]	7	$C_{28}H_{30}N_8O$
58	168–174	C	17	$C_{28}H_{30}N_8O$[b]
(*S*)-**58**	171–174	A	46	$C_{28}H_{30}N_8O$
59	106–110	C	80	$C_{27}H_{29}N_9O \cdot 0.25H_2O$
(*S*)-**59**	105–108	[c]	66	$C_{27}H_{29}N_9O$
(*S*)-**60**	foam	B	6	$C_{27}H_{28}N_8O_2 \cdot 0.25H_2O$
(*S*)-**61**	236–244	B	52	$C_{29}H_{30}N_6OS \cdot 2HCl \cdot 0.5H_2O$
62	foam	A	20	$C_{31}H_{32}N_6O \cdot 1.25H_2O$
(*S*)-**62**	151–152	A	23	$C_{31}H_{32}N_6O$
(*S*)-**63**	107–117	B	30	$C_{30}H_{31}N_7O$
(*S*)-**64**	184–186	A	22	$C_{35}H_{35}N_6O \cdot 2HCl \cdot 0.5H_2O$
65	218–220	A	40	$C_{32}H_{34}N_6O \cdot 3HCl$
66	152–154	C	17	$C_{33}H_{32}N_6O \cdot 0.5H_2O$
67	170–171	[c]	15	$C_{29}H_{32}N_8O \cdot 0.5H_2O$
(*S*)-**67**	170–171	[c]	50	$C_{29}H_{32}N_8O$
68	199–200	C	62	$C_{29}H_{32}N_8O$
69	189–190	C	32	$C_{29}H_{32}N_8O$[b]
70	179–180	C	22	$C_{29}H_{32}N_8O$
71	163–165	C	76	$C_{31}H_{35}N_7O \cdot CH_3SO_3H \cdot 0.5H_2O$
72	104–108	A	2	$C_{34}H_{39}N_7O \cdot 0.5H_2O$
(*S*)-**73**	177–178	B	63	$C_{30}H_{30}N_8O \cdot 0.25H_2O$
(*S*)-**74**	141–144	B	18	$C_{30}H_{31}N_8O_2 \cdot C_4H_4O_4 \cdot H_2O$
(*S*)-**75**	137–138	B	6	$C_{30}H_{31}N_7O_2$
(*S*)-**76**	206–209	A	15	$C_{26}H_{28}F_3N_7 \cdot 2HCl$
77	194–198	A	28	$C_{30}H_{33}N_8O$[d]
78	223–224	[c]	8	$C_{29}H_{32}N_8 \cdot CH_3SO_3H$
79	153–155	[c]	29	$C_{25}H_{29}N_7$
80	150–152	[c]	27	$C_{29}H_{29}N_7O \cdot 0.25H_2O$
81	191–193	[c]	40	$C_{29}H_{30}N_8O \cdot 0.25H_2O$
(*S*)-**82**	168–171	[c]	48	$C_{30}H_{33}N_7O$
83	foam	C	25	$C_{29}H_{29}F_2N_7O \cdot 0.25H_2O$
84	208–211	C	35	$C_{29}H_{29}Cl_2N_7O$[b]
85	208–210	[c]	42	$C_{33}H_{27}N_7O \cdot 2C_4H_4O_4 \cdot 0.5H_2O$
86	202–204	C	42	$C_{17}H_{23}N_7O \cdot 2C_4H_4O_4 \cdot H_2O$
87	227–228	C	34	$C_{30}H_{33}N_7O \cdot 2C_4H_4O_4$
88	184–186	C	81	$C_{24}H_{29}N_7O \cdot 2C_4H_4O_4 \cdot 0.5H_2O$
89	145–155	C	21	$C_{30}H_{31}N_7O_2 \cdot HCl \cdot H_2O$
90	226–229	C	59	$C_{29}H_{29}N_7O \cdot 3HCl$
91	209–215	C	28	$C_{31}H_{33}N_7 \cdot HCl$
92	120–122	C	12	$C_{28}H_{30}N_8O \cdot 2HCl$
93	258–261	C	38	$C_{30}H_{33}N_7O \cdot HCl \cdot H_2O$
94	foam	C	65	$C_{30}H_{33}N_7O \cdot 0.25H_2O$
95	279–281	C	54	$C_{30}H_{32}N_6O \cdot HCl$
96	283–286	C	53	$C_{30}H_{32}N_6O_2 \cdot HCl \cdot 0.25H_2O$
97	178–180	C	74	$C_{30}H_{30}N_6O$
98	186–187	C	33	$C_{30}H_{33}N_7O$
(*S*)-**99**	227–230	A	4	$C_{29}H_{31}N_7O \cdot 3HCl \cdot 0.5H_2O$
(*S*)-**100**	223 dec	B	5	$C_{28}H_{30}N_8 \cdot 4HCl \cdot H_2O$
(*S*)-**101**	172–185	B	6	$C_{27}H_{28}N_8O_2$[b]
(*S*)-**102**	109–113	B	3	$C_{29}H_{30}N_6OS \cdot 0.25H_2O$
(*S*)-**103**	233–236	A	2	$C_{31}H_{32}N_6O \cdot 3HCl \cdot 3H_2O$
(*S*)-**104**	153–137	B	1	$C_{30}H_{31}N_7O \cdot 0.5H_2O$

[a] C, H, and N analyses were within ±0.4% of the theoretical values, unless otherwise noted. [b] Formula determined by high-resolution mass spectral (HRMS) analyses. [c] See the Experimental Section. [d] C: calcd, 69.21; found, 69.99. N: calcd, 21.52; found, 19.65.

ment of the 6-amino group of **5** with 5-membered heterocycles (cf. **57**–**59**, Table 2). In general, however, this increase in potency was accompanied by spontaneous fibrillation at concentrations of ≤1 μM, which was interpreted to be an indication of proarrhythmic side effects, most likely due to Ca^{2+} overload. Occurrence of fibrillation is noted in the tables. Analogs of **56** bearing small, electron-withdrawing groups at the pyrrole 2-position showed increased potency; the cyano [(*S*)-**73**] and formyl [(*S*)-**74**] derivatives were 4- and 15-fold more potent, respectively, than (*S*)-**56**. *No fibrillation was observed for any of the active pyrroles, even the most potent compound,* (*S*)-**74**. Stereoselectivity was also demonstrated in the rabbit heart assay. The *S* enantiomers of compounds **5** and **58** (Table 3) were at least twice as potent as the racemates in ERP and d*P*/d*t* measurements, while no difference was observed between (*S*)-**57** and **57**, and (*S*)-**59** and **59**. In the case of the N3/N9 isomer pairs, a marked increase in potency was observed for the N3 pyrrole (*S*)-**99** compared to its N9 partner (*S*)-**56**. Likewise, the N3 phenyl compound (*S*)-**103** was more potent than (*S*)-**62**, although the difference was not as pronounced. Conversely, in the case of the pyrazoles (*S*)-**100** and (*S*)-**58**, the N9 isomer is significantly more potent than the N3.

Discussion

The in vitro activity of this series of compounds on Na channel inactivation appears to be exquisitely controlled by a number of critical structural features. Despite the apparent diversity in the heterocyclic moieties of reference compounds **1**–**5**, the activity of **5** was significantly diminished upon replacement of the purine nucleus with less nitrogenous analogs (Table 2). Preliminary calculations of electrostatic potential surfaces among the heterocyclic nuclei gave no insight into this activity trend. The purine series was selected for this study, in part, on the basis of synthetic accessibility.

The presence of the BHP and amino-2-propanol groups in the side chain present in each of the reference agents **1**–**5** raised a concern for the specificity of these compounds for the desired Na channel activity.[15] Compound **1** was screened through radioligand binding assays for 12 different receptors and at a concentration of 10 μM demonstrated >75% inhibition of binding at histamine (H_1), nitrendipine, opiate (nonselective), seratonin (nonselective), muscarinic (nonselective), dopamine (D_2), and α_1-, α_2-, and β-adrenergic sites.[39] We hoped to minimize such ancillary receptor interactions by making modifications to the BHP and the chain connecting the BHP to the purine. Unfortunately, very few structural changes could be made to the BHP moiety without significant loss of Na channel activity, and none of these analogs retained the potency of the initial comparitor, **56** (Table 5). The hydroxyl group on the connecting chain of **56** also appears to play a critical role in Na channel activity, as its removal leads to complete loss of activity. The H-bond donor properties of the hydroxyl group are mimicked by the amino compound **78**, the only hydroxyl modification retaining comparable activity (Table 4).

The 6-position of the purine ring tolerated a modest variety of substituents, and the activities seem to correlate with a pocket in the molecular target for a planar substituent of finite size. Electronic contributions of this group to the purine ring are not critical, as the NH_2 (donor), CN (acceptor), and H (neutral) analogs (**5**, **53**, and **51**, respectively) possess the same range of

potency. Na channel activity does appear to be a sensitive function of the size of the purine 6-substituent. Potency in both the oocyte and Langendorff rabbit heart assays is maximized by the presence of a 5-membered heterocycle at the purine 6-position (**56**–**59**). While the 6-membered heterocyclic analogs such as phenyl (**62**) and 4-pyridinyl [(*S*)-**62**] are active, they are less potent than the 5-membered azoles. Size alone, however, is an insufficient descriptor for this activity trend. The lack of potency in the oxadiazole (*S*)-**60** was surprising, and although we anticipated the 2-thienyl analog (*S*)-**61** to be of comparable potency to the phenyl derivative, the activity of (*S*)-**61** resembled that of the more potent azoles. Groups larger than phenyl at the purine 6-position are detrimental to activity; the naphthyl (**64**), benzyl (**65**), benzylamino (**54**), phenylethynyl (**66**), 1-piperidinyl (**55**), and tetrahydroindole (**72**) analogs were all inactive. Methyl substitution at various positions of the azole and pyrrole rings decreased or abolished activity of the unsubstituted comparitors (**67**–**71**), which supports the hypothesis for a size restriction at this position. Interestingly, small, electron-withdrawing substituents at the pyrrole 2-position (CHO and CN) increased potency. The 2-formylpyrrole (*S*)-**74** is the most active compound of the series in both the oocyte and Langendorff heart assays.

Conclusions

A series of purine-based Na channel inactivation modifiers has been synthesized and evaluated on cardiac Na channels expressed in *Xenopus* oocytes. The addition of a 5-membered heterocyclic ring at the purine 6-position increased the activity of these compounds at the Na channel, which translated into antiarrhythmic and inotropic activities in a functional in vitro assay. A few representative compounds [(*S*)-**99**, (*S*)-**57**, (*S*)-**58**, and (*S*)-**59**] were tested for antiarrhythmic efficacy by measuring ERP changes in a paced cat model.[40] In vivo activity was demonstrated after intravenous infusion; however, only (*S*)-**99** increased refractoriness (by 18–26 ms at a cumulative dose of 1 mg/kg with a duration of ≥90 min postinfusion) without inducing fibrillation at doses just above the activity threshold. The most promising compound based on its in vitro profile is the formylpyrrole (*S*)-**74**, which increased ERP and d*P*/d*t* in the Langendorff rabbit heart at very low concentrations without causing the fibrillation often observed with compounds acting via this mechanism.[41]

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected. Proton NMR (GE QE300 or JOEL GSX-270 spectrometer), IR (Nicolet 10DX or 550 FT-IR spectrophotometer), UV (Gilford Response spectrophotometer), and mass spectra (Kratos Concept or Nermag R10-10C spectrometer) were consistent with the assigned structures. HMBC and HMQC experiments were performed on a Bruker AMX-500 or AMX-360 NMR spectrometer. ^{1}H NMR multiplicity data are denoted by s (singlet), d (doublet), dd (doublet of doublets), t (triplet), m (multiplet), and br (broad). Coupling constants are in hertz (Hz). Infrared spectra (IR) were measured as 1% KBr pellets. Optical rotations were determined with a Rudolph Research automatic polarimeter 3. Carbon, hydrogen, and nitrogen elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ, and are within ±0.4% of theoretical values. Nonaqueous reactions were generally carried out under a N_2 or Ar atmosphere.

(*S*)-1-(Diphenylmethyl)-4-(2,3-epoxypropyl)piperazine [(*S*)-7]. (*S*)-2,3-Epoxypropyl 3-nitrobenzenesulfonate (9.6 g, 39.7 mmol)[42] was added to a slurry of benzhydrylpiperazine (10 g, 39.7 mmol) and milled K_2CO_3 (2 g, 51.6 mmol) in DMSO (50 mL) and stirred at room temperature for 18 h. The solution was poured into water (1 L) and extracted three times with EtOAc (200 mL). The organics were dried over $MgSO_4$ and then concentrated under vacuum to give an oil (10 g) which was purified by silica gel chromatography (2% MeOH/CH_2Cl_2 eluent) to afford 8.3 g (68%) of the product (*S*)-**7**: mp 91–93 °C; $[\alpha]_D = -13.2°$ (c = 1, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, J = 7.89 Hz, 4H), 7.25 (t, J = 7.30 Hz, 4H), 7.16 (t, J = 6.49 Hz, 2H), 4.25 (s, 1H), 3.27 (m, 1H), 2.73 (dd, J_1 = 4.91 Hz, J_2 = 3.33 Hz, 1H), 2.46 (m, 9H).

(*R*)-1-(Diphenylmethyl)-4-(2,3-epoxypropyl)piperazine [(*R*)-7]: prepared from (*R*)-2,3-epoxypropyl 3-nitrobenzenesulfonate (9.6 g, 39.7 mmol)[42] following the same procedure as for (*S*)-**7**; mp 114–117 °C; $[\alpha]_D = +13.4°$ (c = 1, MeOH).

6-(2-Thienyl)-1*H*-purine (14). Method D. This procedure illustrates the general method for preparation of **12**–**14** using the appropriate Grignard reagent and either **31**[43] or **32**[13] as the starting materials. A 2 M ethereal solution of 2-thienylmagnesium bromide, made under standard conditions (4.19 mL, 8.38 mmol), was added via cannula to **31** (1.0 g, 4.19 mmol) and $NiCl_2$(dppp) (0.34 g, 0.63 mmol) in dry THF (40 mL). After heating under reflux for 2 h, the reaction mixture was stirred at room temperature for 18 h. The solution was poured into water (50 mL) and extracted three times with EtOAc (100 mL). The organics were separated and washed quickly with 2 N HCl (50 mL) and saturated sodium bicarbonate solution (50 mL). The EtOAc solution was then dried over $MgSO_4$ and concentrated under vacuum to yield the crude solid. Purification through a silica gel column (40% EtOAc/hexanes eluent) afforded 800 mg (67%) of the N-THP analog which was stirred in THF (10 mL) and 2 N HCl (4 mL) for 20 h. The precipitate was removed, washed with water, and then dried under vacuum at 60 °C to afford 390 mg (69%, 46% overall yield) of **14**: mp 312–315 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.60 (s, 2H), 7.86 (d, J = 4.85 Hz, 1H), 7.30 (t, J = 4.29 Hz, 1H). Anal. ($C_9H_6N_4S$) C, H, N.

6-(1*H*-Pyrazol-1-yl)-1*H*-purine (18). Method E. This procedure illustrates the general method for preparation of **15** and **17-21** using the appropriate 1*H*-azole. 6-Chloropurine (9.3 g, 60.2 mmol) and pyrazole (22.0 g, 0.323 mol) were heated together in a 150 °C oil bath until the melted mixture solidified (30 min). After cooling, CH_2Cl_2 was added, and the precipitate was removed and washed with CH_2Cl_2. Recrystallization from DMF afforded 10.6 g (95%) of **18**: mp 312–322 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.88 (s, 1H), 8.80 (s, 1H), 8.63 (s, 1H), 8.06 (s, 1H), 6.72 (dd, $J_1 = J_2$ = 2.10 Hz, 1H). Anal. ($C_8H_6N_6$) C, H, N.

6-(2-Methyl-1*H*-imidazol-1-yl)-1*H*-purine (16). A slurry of 6-chloropurine (7.73 g, 50 mmol) and 2-methylimidazole (16.4 g, 0.20 mol) in *n*-butanol (45 mL) was heated under reflux for 1 h. After cooling, the precipitate was collected and washed with EtOH, CH_3CN, and Et_2O to afford 8.35 g (84%) of **16**. An analytical sample was recrystallized from DMF: mp 310–312 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.74 (s, 1H), 8.42 (s, 1H), 7.03 (s, 1H), 2.75 (s, 3H). Anal. ($C_9H_8N_6$) C, H, N.

6-(1*H*-Pyrrol-1-yl)-1*H*-purine (23). Method F. This procedure illustrates the general method for preparation of **23**–**26**. The 2,5-dimethoxytetrahydrofuran used in the preparation of **23** was replaced with 2,5-hexanedione for **24**, 2-(2-oxopropyl)cyclohexanone[44] for **25**, and 2,5-dimethoxy-3-tetrahydrofurancarboxaldehyde for **26**. Adenine (250 g, 1.85 mol) and 2,5-dimethoxytetrahydrofuran (263 mL, 2.04 mol) were dissolved in AcOH (750 mL) and heated under reflux for 1 h. After cooling, the precipitate was removed and washed with Et_2O. Drying under vacuum at 100 °C afforded 115 g (34%) of **23**: mp 304–306 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.56 (s, 1H), 8.28 (dd, $J_1 = J_2$ = 2.02 Hz, 2H), 6.39 (dd, $J_1 = J_2$ = 2.18 Hz, 2H). Anal. ($C_9H_7N_5$) C, H, N.

1-(1*H*-Purin-6-yl)-1*H*-pyrrole-2-carbonitrile (27). A solution of **23** (1.85 g, 10.0 mmol), 3,4-dihydro-2*H*-pyran (925 mg, 11.0 mmol), and *p*-toluenesulfonic acid monohydrate (50

mg, 0.26 mmol) in EtOAc (20 mL) was heated under reflux for 17 h. The cooled mixture was filtered through Celite and washed with saturated sodium bicarbonate solution. The organics were dried over $MgSO_4$ and then concentrated under vacuum to give 2.64 g (98%) of 6-(1*H*-pyrrol-1-yl)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine, of which 1.64 g (6.10 mmol) was suspended in CH_3CN (50 mL) at −20 °C. Chlorosulfonyl isocyanate (1.29 g, 9.14 mmol) was added dropwise. After stirring for 15 min at −20 °C, DMF (1.6 mL, 20.7 mmol) was added, the mixture was warmed to room temperature, and saturated sodium bicarbonate solution (25 mL) was added. The solution was extracted with EtOAc (50 mL), dried over $MgSO_4$, and then concentrated under vacuum to give a solid that was suspended in 2 N HCl (25 mL). After stirring for 2.5 h, the precipitate was removed, washed with water, and dried under vacuum to afford 1.05 g (82%) of **27**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.74 (m, 1H), 8.68 (s, 1H), 7.39 (m, 1H), 6.62 (m, 1H).

1-(1*H*-Purin-6-yl)-1*H*-pyrrole-2-carboxaldehyde (28). To DMF (15 mL, 0.194 mol) at 0 °C was added $POCl_3$ (4.97 g, 32.4 mmol) dropwise. After stirring for 30 min at 0 °C, a solution of **23** (5.0 g, 27.0 mmol) in DMF (50 mL) was added slowly. The solution was then warmed to 50 °C for 20 h and poured into saturated sodium bicarbonate solution (50 mL). The pH was adjusted to approximately 6 with 2 N HCl, and the precipitate was removed and dried under vacuum at 60 °C to afford 4.6 g (80%) of **28**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.18 (s, 1H), 8.83 (s, 1H), 8.65 (s, 1H), 8.26 (s, 1H), 7.23 (m, 1H), 6.58 (m, 1H).

6-(1,2,4-Oxadiazol-3-yl)-1*H*-purine (29). A mixture of **32**[13] (10.4 g, 43.6 mmol) and potassium cyanide (4.3 g, 65.4 mmol) in DMSO (50 mL) was stirred at 120 °C for 6 h. The solution was poured into water (500 mL) and extracted three times with EtOAc (150 mL). The organics were dried over $MgSO_4$ and then concentrated under vacuum to give an oil (5 g) which was chromatographed over silica gel with 2% MeOH/CH_2Cl_2 to afford 3.2 g (32%) of the 6-cyano analog **36**. To a solution of hydroxylamine hydrochloride (1.62 g, 23.6 mmol) in EtOH (80 mL) was added milled potassium hydroxide (1.62 g, 28.9 mmol). After heating under reflux for 45 min, the potassium chloride was filtered and crude **36** (1.3 g, 5.68 mmol) was added to the solution. After 45 min, the solution was cooled to 0 °C, and the precipitate was removed to afford 1.4 g (94%) of the 6-amidoxime. This was then slurried in triethyl orthoformate (15 mL, 90.3 mmol), and *p*-toluenesulfonic acid monohydrate (5 mg, 0.03 mmol) was added. After heating under reflux for 2 h, the precipitate was removed, recrystallized from DMF, and washed with Et_2O to afford 0.64 g (51%, 15% overall yield) of **29**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.78 (br, 1H), 9.97 (s, 1H), 9.11 (s, 1H), 8.76 (s, 1H).

6-(4-Pyridinyl)-1*H*-purine (30). To a cooled (0 °C) solution of aniline (24.13 g, 0.259 mol) in concentrated HCl (85 mL) and water (260 mL) was added a solution of sodium nitrite (18.23 g, 0.264 mol) in water (72 mL). After stirring for 30 min at 0 °C, this solution was added to **37**[27] (50.0 g, 0.259 mol) and sodium acetate (115 g, 1.40 mol) in water (200 mL). After stirring for 90 min at room temperature, the mixture was partially concentrated, and EtOAc (300 mL) was added. The organics were washed with water and then saturated sodium bicarbonate solution, dried over $MgSO_4$, and then concentrated under vacuum to afford 76 g (99%) of the diazo intermediate **38**. A solution of sodium ethoxide was prepared from sodium (9.68 g, 0.421 mol) in EtOH (150 mL) and to this was added thiourea (32.0 g, 0.321 mol) in EtOH (350 mL), followed by **38** (50.0 g, 0.168 mol) in EtOH (150 mL). After heating under reflux for 48 h, the solvent was evaporated under vacuum and the residue was dissolved in water (250 mL). The solution was neutralized with 2 N HCl; the precipitate was removed and suspended in water (750 mL) and concentrated ammonium hydroxide (150 mL). Raney nickel (20 g) was added, and the mixture was heated under reflux for 18 h. The hot mixture was filtered through Celite and then concentrated under vacuum to afford 16.05 g (51%) of 5-amino-6-(pyridin-4-yl)-4(3*H*)-pyrimidone (**39**): ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.59 (d, J = 5.10 Hz, 2H), 7.71 (d, J = 5.58 Hz, 2H), 7.71 (s, 1H), 5.37 (br, 2H).

A mixture of **39** (3.50 g, 18.6 mmol) and 3 Å sieves (3 g) was suspended in benzaldehyde (38 mL, 0.372 mol) and heated to 150 °C for 18 h. After cooling, the mixture was diluted with Et_2O (100 mL), the sieves were filtered, and the precipitate (**40**) was removed. The crude **40** was washed with Et_2O, dried under vacuum at 60 °C, and suspended in $POCl_3$ (50 mL). The mixture was heated under reflux for 30 min and filtered through Celite with CH_2Cl_2 washing. The filtrate was concentrated and carefully quenched with NH_4OH and ice. The organics were extracted with EtOAc (50 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was dissolved in 2 N HCl (50 mL) and extracted with Et_2O (50 mL). The organics were basified with 5 N NaOH, extracted with EtOAc, dried over $MgSO_4$, and then concentrated under vacuum to afford 2.38 g (62%) of 5-amino-4-chloro-6-(4-pyridinyl)pyrimidine (**41**): ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.71 (d, J = 5.08 Hz, 2H), 8.33 (s, 1H), 7.67 (d, J = 6.20 Hz, 2H), 5.79 (br, 2H).

To a solution of **41** (2.38 g, 11.5 mmol) in EtOH (35 mL) was added concentrated NH_4OH (35 mL), and the reaction mixture was heated to 150 °C for 16 h. The precipitate was removed and dried under vacuum at 60 °C to afford 1.25 g (58%) of 4,5-diamino-6-(4-pyridinyl)pyrimidine (**42**). Cyclization was effected by heating a portion of **42** (1.0 g, 5.35 mmol) in formamide (10 mL) at 150 °C for 21 h. Water (25 mL) was added, and the precipitate was removed and dried under vacuum at 60 °C to afford 985 mg (94%, 17% overall yield) of **30**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.00 (s, 1H), 8.81 (d, J = 4.40 Hz, 2H), 8.73 (s, 1H), 8.64 (d, J = 3.54 Hz, 2H).

(*S*)-α-[[4-(Diphenylmethyl)-1-piperazinyl]methyl]-6-(1*H*-pyrrol-1-yl)-9*H*-purine-9-ethanol [(*S*)-56] and (*S*)-α-[[4-(Diphenylmethyl)-1-piperazinyl]methyl]-6-(1*H*-pyrrol-1-yl)-3*H*-purine-3-ethanol [(*S*)-99]. Method A. This procedure illustrates the general method for preparation of **5**, (*S*)-**5**, (*R*)-**5**, **46**, **54**–**56**, (*S*)-**56**, (*R*)-**56**, (*S*)-**58**, **62**, (*S*)-**62**, (*S*)-**64**, **65**, **72**, (*S*)-**76**, **77**,[45] (*S*)-**99**, and (*S*)-**103**. To a solution of **23** (1.63 g, 8.83 mmol) and (*S*)-**7** (2.72 g, 8.83 mmol) in 1,4-dioxane (25 mL) was added 1 N NaOH (5 mL), and the mixture was heated under reflux for 16 h. The solution was poured into water (100 mL) and extracted three times with EtOAc (150 mL). The organics were dried over $MgSO_4$ and then concentrated under vacuum to give a foam (4.5 g) which was chromatographed over silica gel with 1% MeOH/CH_2Cl_2. The first product eluted was recrystallized in EtOH to afford 730 mg (17%) of (*S*)-**56**: mp 156–158 °C; $[\alpha]_D$ = +3.7° (c = 1, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.33 (dd, $J_1 = J_2$ = 2.07 Hz, 2H), 8.20 (s, 1H), 7.37 (d, J = 6.32 Hz, 4H), 7.25 (t, J = 7.18 Hz, 4H), 7.18 (t, J = 5.44 Hz, 2H), 6.42 (dd, $J_1 = J_2$ = 2.15 Hz, 2H), 4.45 (dd, J_1 = 14.1 Hz, J_2 = 1.13 Hz, 1H), 4.20 (dd, J_1 = 7.33 Hz, J_2 = 5.64 Hz, 1H), 4.18 (s, 1H), 4.07 (m, 1H), 2.61 (m, 2H), 2.34 (m, 8H). Anal. ($C_{29}H_{31}N_7O$) C, H, N.

The second product eluted was recrystallized in EtOAc/hexanes to afford 181 mg (4%) of (*S*)-**99**: mp 164–168 °C; $[\alpha]_D$ = +23.1° (c = 1, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.36 (dd, $J_1 = J_2$ = 2.12 Hz, 2H), 8.28 (s, 1H), 7.38 (d, J = 6.68 Hz, 4H), 7.26 (t, J = 7.41 Hz, 4H), 7.16 (t, J = 5.48 Hz, 2H), 6.44 (dd, $J_1 = J_2$ = 2.16 Hz, 2H), 4.79 (dd, J_1 = 11.84 Hz, J_2 = 1.14 Hz, 1H), 4.34 (dd, J_1 = 12.41 Hz, J_2 = 6.20 Hz, 1H), 4.22 (m, 1H), 4.17 (s, 1H), 2.45 (m, 10H). Anal. ($C_{29}H_{31}N_7O$) C, H, N.

(*S*)-α-[[4-(Diphenylmethyl)-1-piperazinyl]methyl]-6-(2-thienyl)-9*H*-purine-9-ethanol [(*S*)-61] and (*S*)-α-[[4-(Diphenylmethyl)-1-piperazinyl]methyl]-6-(2-thienyl)-3*H*-purine-3-ethanol [(*S*)-102]. Method B. This procedure illustrates the general method for preparation of (*S*)-**52**, (*S*)-**60**, (*S*)-**61**, (*S*)-**63**, (*S*)-**73**, (*S*)-**74**, (*S*)-**75**, (*S*)-**100**, (*S*)-**101**, (*S*)-**102**, and (*S*)-**104**. A solution of **14** (1.07 g, 5.30 mmol) and (*S*)-**7** (1.63 g, 5.30 mmol) in DMSO (10 mL) was heated to 130 °C for 12 h. The solution was poured into water (100 mL), saturated with NaCl, and extracted three times with EtOAc (100 mL). The organics were dried over $MgSO_4$ and then concentrated under vacuum to give a foam which was chromatographed over silica gel with EtOAc to give 1.4 g (52%) of crude (*S*)-**61**. The HCl salt was prepared by dissolving in EtOAc and adding ethereal HCl. The precipitate was collected

and recrystallized from EtOH to afford 0.60 g (19%) of (*S*)-**61** as the dihydrochloride hemihydrate: mp 236–244 °C; $[\alpha]_D$= +1.2° (*c* = 1, CH_2Cl_2);[46] ^1H NMR (300 MHz, DMSO-d_6) δ 8.82 (s, 1H), 8.61 (d, *J* = 3.55 Hz, 1H), 8.57 (s, 1H), 7.89 (d, *J* = 5.13 Hz, 1H), 7.33 (m, 11H), 4.32 (m, 4H), 3.37 (m, 10H). Anal. ($C_{29}H_{30}N_6OS$·2HCl·0.5H_2O) C, H, N.

The silica gel column was then eluted with 5% MeOH/CH_2Cl_2 to yield a foam which was crystallized in MeOH to afford 70 mg (3%) of (*S*)-**102**: mp 109–113 °C; $[\alpha]_D$ = +16.4° (*c* = 0.25, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 8.77 (d, *J* = 3.67 Hz, 1H), 8.54 (s, 1H), 8.39 (s, 1H), 7.71 (d, *J* = 4.67 Hz, 1H), 7.39 (d, *J* = 7.36 Hz, 4H), 7.27 (t, *J* = 8.41 Hz, 4H), 7.17 (t, *J* = 7.16 Hz, 2H), 4.82 (dd, J_1 = 11.92 Hz, J_2 = 1.52 Hz, 1H), 4.37 (dd, J_1 = 13.38 Hz, J_2 = 6.30 Hz, 1H), 4.26 (m, 1H), 4.17 (s, 1H), 2.45 (m, 10H). Anal. ($C_{29}H_{30}N_6OS$·0.25H_2O) C, H, N.

(*S*)-α-[[4-(Diphenylmethyl)-1-piperazinyl]methyl]-6-(1*H*-pyrrol-1-yl)-9*H*-purine-9-ethanol [(*S*)-56]. Method C. This procedure illustrates the general method for preparation of **53**, **57–59**, **66**, **68–71**, **83–84**, and **86–98**. Purine **23** used in the preparation of (*S*)-**56** was replaced with appropriate purines to prepare **53**, **57–59**, **66**, and **68–71**. The benzhydrylpiperazine used in the preparation of (*S*)-**56** was replaced with the appropriate piperazine or piperidine for **83**, **84**,[47] **86**, **87**,[48] **88**, **89**,[49] **90**,[50] **91**,[51] **92**,[52] **93**,[53] **94**,[54] **95**,[55] **96**, **97**,[56] and **98**.[57] To a slurry of **23** (5.0 g, 27.0 mmol), triphenylphosphine (7.1 g, 27.0 mmol), and (*R*)-glycidol[19] (2.7 mL, 40.8 mmol) in THF (200 mL) at 0 °C was added diethyl diazodicarboxylate (5.6 g, 32.2 mmol) in THF (50 mL). After stirring at 0 °C for 3 h, the mixture was warmed to room temperature overnight and then filtered. The filtrate was concentrated under vacuum, dissolved in CH_2Cl_2 (20 mL), and flash chromatographed through silica gel (EtOAc eluent). After concentrating under vacuum, the solids were washed with cold Et_2O followed by cold MeOH to afford 4.2 g (65%) of the intermediate epoxide (*S*)-**10a**: mp 152–154 °C dec; $[\alpha]_D$ = +37.2° (*c* = 1, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.32 (dd, J_1 = J_2 = 2.13 Hz, 2H), 8.11 (s, 1H), 6.44 (dd, J_1 = J_2 = 2.15 Hz, 2H), 4.71 (dd, J_1 = 14.66, J_2 = 3.38 1H), 4.23 (dd, J_1 = 12.97, J_2 = 5.08 1H), 3.38 (m, 1H), 2.89 (t, 1H), 2.52 (m, 1H). Anal. ($C_{12}H_{11}N_5O$) C, H, N.

A solution of (*S*)-**10a** (500 mg, 2.07 mmol) and benzhydrylpiperazine (630 mg, 2.50 mmol) in EtOH (20 mL) was heated under reflux for 3 h. The solution was concentrated under vacuum and flash chromatographed (EtOAc eluent), and the product was recrystallized in EtOAc/hexanes to afford 600 mg (61%) of (*S*)-**56**: mp 156–158 °C; $[\alpha]_D$ = +3.2° (*c* = 1, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.33 (dd, J_1 = J_2 = 2.07 Hz, 2H), 8.20 (s, 1H), 7.37 (d, *J* = 6.32 Hz, 4H), 7.25 (t, *J* = 7.18 Hz, 4H), 7.18 (t, *J* = 5.44 Hz, 2H), 6.42 (dd, J_1 = J_2 = 2.15 Hz, 2H), 4.45 (dd, J_1 = 14.1 Hz, J_2 = 1.13 Hz, 1H), 4.20 (dd, J_1 = 7.33 Hz, J_2 = 5.64 Hz, 1H), 4.18 (s, 1H), 4.07 (m, 1H), 2.61 (m, 2H), 2.34 (m, 8H). Anal. ($C_{29}H_{31}N_7O$) C, H, N.

(*R*)-α-(Chloromethyl)-6-(1*H*-pyrrol-1-yl)-3*H*-purine-3-ethanol [(*R*)-43]. A slurry of **23** (8.0 g, 43.0 mmol) and (*R*)-epichlorohydrin (9.0 g, 97.3 mmol) in AcOH (50 mL) was heated under reflux until the solids dissolved (20 min). After cooling, the precipitate was removed, washed with CH_2Cl_2, and recrystallized from EtOAc/hexanes to afford 3.75 g (41%) of (*R*)-**43**: mp 280 °C dec; $[\alpha]_D$ = +76.5° (*c* = 0.5, MeOH); ^1H NMR (300 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.36 (dd, J_1 = J_2 = 2.14 Hz, 2H), 8.29 (s, 1H), 6.47 (dd, J_1 = J_2 = 2.24 Hz, 2H), 4.81 (dd, J_1 = 12.41, J_2 = 1.69, 1H), 4.40 (dd, J_1 = 11.28, J_2 = 9.59, 1H), 4.34 (m, 1H), 3.79 (dd, J_1 = 12.40, J_2 = 4.51, 1H), 3.71 (dd, J_1 = 12.40, J_2 = 4.51, 1H). Anal. ($C_{12}H_{12}ClN_5O$) C, H, N.

(*R*)-3-(Oxiranylmethyl)-6-(1*H*-pyrrol-1-yl)-3*H*-purine [(*R*)-44]. To a suspension of (*R*)-**43** (1.47 g, 5.58 mmol) in water (100 mL) was added NaOH (2.5 g, 62.5 mmol). After stirring for 2 h, EtOAc (50 mL) was added. The organics were separated, dried over $MgSO_4$, and concentrated under vacuum to give a mixture of oil and solids (1.1 g) which was chromatographed over silica gel with 2% MeOH/CH_2Cl_2. The solids were recrystallized from EtOAc/hexanes to afford 390 mg (29%) of (*R*)-**44**: mp 118 °C dec; $[\alpha]_D$ = +30.7° (*c* = 0.25, MeOH); ^1H NMR (300 MHz, DMSO-d_6) δ 8.84 (s, 1H), 8.36 (dd, J_1 = J_2 = 2.14 Hz, 2H), 8.29 (s, 1H), 6.47 (dd, J_1 = J_2 = 2.24 Hz, 2H), 4.88 (dd, J_1 = 12.41, J_2 = 3.95, 1H), 4.64 (dd, J_1 = 13.54, J_2 = 5.64, 1H), 3.61 (m, 1H), 2.85 (t, 1H), 2.64 (m, 1H). Anal. ($C_{12}H_{11}N_5O$) C, H, N.

Conversion of (*R*)-43 to (*S*)-99. To a suspension of 60% NaH (0.35 g, 8.75 mmol) in DMSO (5 mL) was added benzhydrylpiperazine (2.22 g, 8.8 mmol) in DMSO (10 mL). After stirring for 30 min at 60 °C, the slurry was added to (*R*)-**43** (2.22 g, 8.0 mmol) in DMSO (20 mL) at 120 °C, stirred for 15 min, and cooled to room temperature. The mixture was poured into water (400 mL) and extracted three times with EtOAc (100 mL). The organics were dried over $MgSO_4$ and then concentrated under vacuum to give a foam (4 g) which was purified by silica gel chromatography (5% MeOH/CH_2Cl_2 eluent) to give (*S*)-**99**. The HCl salt was prepared by dissolving the residue in EtOAc and adding ethereal HCl. The precipitate was collected and recrystallized from MeOH/Et_2O to afford 2.1 g (43%) of (*S*)-**99** as the trihydrochloride monohydrate: mp 222–224 °C; $[\alpha]_D$ = +4.7° (*c* = 0.5, MeOH); ^1H NMR (300 MHz, DMSO-d_6) δ 9.20 (s, 1H), 8.90 (s, 1H), 8.29 (s, 2H), 7.84 (br, 4H), 7.35 (m, 6H), 6.58 (s, 2H), 4.90 (d, *J* = 10.15 Hz, 1H), 4.64 (m, 2H), 3.68 (m, 6H), 3.29 (m, 5H). Anal. ($C_{29}H_{31}N_7O$·3HCl·H_2O) C, H, N.

Determination of the Enantiomeric Purity of 56. The optimum resolution of the ^1H NMR spectrum of 10 mg (20.2 μmol) of (±)-**56** in 1.0 mL of $CDCl_3$ in the presence of 500 μL of 10^{-3} M Eu(tfc)$_3$ gave two sharp singlets (δ 8.66 and 8.62, separated by 11.9 Hz) of equal intensity for the purine C8 proton. A sample of (*R*)-**56**, prepared from (*R*)-**7** using method A, and the same concentration of Eu(tfc)$_3$ gave only a singlet at δ 8.59, which would correspond to a >95% ee. The ^1H NMR spectra of both enantiomers of **56**, prepared from optically enriched glycidols[19] using method C, were obtained in the same manner. It was determined that both (*R*)- and (*S*)-**56** from method C were approximately 80% ee from NMR integration, which was similar to the enantiomeric purity of the starting glycidols.

(*S*)-α-[[4-(Diphenylmethyl)-1-piperazinyl]methyl]-6-(1*H*-imidazol-1-yl)-9*H*-purine-9-ethanol [(*S*)-57]. To a solution of (*S*)-**7** (3.79 g, 12.3 mmol) and **15** (2.29 g, 12.3 mmol) in DMSO (35 mL) was added 60% NaH (590 mg, 14.8 mmol) in portions. After heating at 140 °C for 20 h, the suspension was cooled and poured into water (200 mL). The organics were extracted with CH_2Cl_2 (100 mL), dried over $MgSO_4$, and then concentrated under vacuum to give an oil which was chromatographed over silica gel with 2% MeOH/CH_2Cl_2. Recrystallization from MeOH afforded 430 mg (8%) of (*S*)-**57**: mp 178–180 °C; $[\alpha]_D$ = −2.9° (*c* = 1, $CHCl_3$); ^1H NMR (300 MHz, DMSO-d_6) δ 9.15 (s, 1H), 8.76 (s, 1H), 8.20 (s, 1H), 8.38 (s, 1H), 8.29 (s, 1H), 7.37 (d, *J* = 7.20 Hz, 4H), 7.22 (m, 7H), 4.49 (dd, J_1 = 11.45 Hz, J_2 = 2.82 Hz, 1H), 4.21 (dd, J_1 = 8.24 Hz, J_2 = 6.78 Hz, 1H), 4.19 (s, 1H), 4.08 (m, 1H), 2.63 (m, 2H), 2.38 (m, 8H). Anal. ($C_{28}H_{30}N_8O$·0.25H_2O) C, H, N.

α-[[4-(Phenylmethyl)-1-piperazinyl]methyl]-6-(1*H*-pyrrol-1-yl)-9*H*-purine-9-ethanol (85). A solution of **23** (5.0 g, 27.0 mmol), benzyl-4-(2,3-epoxypropyl)-piperazine (prepared from benzylpiperazine via the same procedure as for **7**;[16] 6.2 g, 27.0 mmol), 1.1 M tetrabutylammonium fluoride in THF (3.0 mL, 3.3 mmol), and 1,4-dioxane (30 mL) was heated under reflux for 4 h. The solution was concentrated under vacuum and chromatographed over silica gel eluting with 20% EtOAc/CH_2Cl_2 and then 20% EtOH/CH_2Cl_2 to yield 4.3 g of crude **85**. The fumarate salt was prepared by dissolving **85** in acetone and adding fumaric acid (2.3 g, 20.3 mmol). The precipitate was collected and recrystallized from acetone/MeOH to afford 5.0 g (28%) of **85** as the difumarate hemihydrate: mp 208–210 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 8.77 (s, 1H), 8.59 (s, 1H), 8.37 (dd, J_1 = J_2 = 2.02 Hz, 2H), 7.36 (m, 5H), 6.65 (s, 4H), 6.46 (dd, J_1 = J_2 = 2.02 Hz, 2H), 4.44 (d, *J* = 12.15 Hz, 1H), 4.20 (m, 2H), 3.52 (s, 2H), 2.55 (m, 10H). Anal. ($C_{23}H_{27}N_7O$·2$C_4H_4O_4$) C, H, N.

6-Chloro-α-[[4-(diphenylmethyl)-1-piperazinyl]methyl]-9*H*-purine-9-ethanol (51). This compound was prepared from 6-chloropurine and **7**[16] in 61% yield via the same procedure as for **85**. The hemifumarate salt was recrystallized

from MeOH: mp 181–183 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.61 (s, 1H), 7.42 (d, J = 6.09 Hz, 4H), 7.30 (t, J = 6.10 Hz, 4H), 7.21 (t, J = 6.26 Hz, 2H), 6.63 (s, 2H), 4.42 (d, J = 10.15 Hz, 1H), 4.13 (s, 1H), 4.18 (m, 2H), 2.45 (m, 6H), 2.22 (m, 4H); LSIMS-HRMS calcd for $C_{25}H_{27}ClN_6O$ $(M + H)^+$ 463.2013, found 463.2010.

(*S*)-α-[[4-(Diphenylmethyl)-1-piperazinyl]methyl]-6-(2-methyl-1*H*-imidazol-1-yl)-9*H*-purine-9-ethanol [(*S*)-67]. A solution of (*S*)-51 (840 mg, 1.81 mmol), prepared from 6-chloropurine and (*S*)-7 via the same procedure as for **51**, and 2-methylimidazole (1.0 g, 12.3 mmol) in *n*-butanol (2 mL) was heated to reflux, allowing the *n*-butanol to evaporate. After heating to 130 °C, the mixture was cooled and partitioned between CH_2Cl_2 and water, and the organics were filtered through a charcoal pad. After concentrating under vacuum, the oil was washed with hot hexanes and crystallized from CH_3CN. Recrystallization from CH_3CN afforded 458 mg (50%) of (S)-**67**: mp 170–171 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.48 (s, 1H), 8.31 (s, 1H), 7.37 (d, J = 6.44 Hz, 4H), 7.23 (m, 6H), 6.92 (d, J = 3.89 Hz, 1H), 4.54 (d, J = 12.35 Hz, 1H), 4.20 (s, 1H), 4.18 (m, 2H), 2.82 (s, 3H), 2.63 (m, 2H), 2.40 (m, 8H). Anal. ($C_{29}H_{32}N_8O$) C, H, N.

(*S*)-α-[[4-(Diphenylmethyl)-1-piperazinyl]methyl]-6-(1*H*-1,2,4-triazol-1-yl)-9*H*-purine-9-ethanol [(*S*)-59]. This compound was prepared from **21** and (*S*)-7 in 66% yield via the same procedure as for **85**, using DMF as the solvent instead of 1,4-dioxane. The product was recrystallized from MeOH: mp 105–108 °C; $[\alpha]_D$ = +10.3° (c = 0.5, DMF); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (s, 1H), 8.87 (s, 1H), 8.40 (s, 1H), 8.28 (s, 1H), 7.32 (d, J = 7.37 Hz, 4H), 7.25 (t, J = 7.42 Hz, 4H), 7.16 (t, J = 7.25 Hz, 2H), 4.50 (dd, J_1 = 11.6 Hz, J_2 = 2.71 Hz, 1H), 4.26 (dd, J_1 = 7.95 Hz, J_2 = 6.27 Hz, 1H), 4.20 (s, 1H), 4.09 (m, 1H), 2.65 (m, 2H), 2.40 (m, 8H). Anal. ($C_{27}H_{29}N_9O$) C, H, N.

α-[[4-(Diphenylmethyl)-1-piperazinyl]methyl]-6-(2-methyl-1*H*-imidazol-1-yl)-9*H*-purine-9-ethanol (67). To a solution of **16** (2.0 g, 10.0 mmol) and **7** (3.1 g, 10.0 mmol) in 1,4-dioxane (50 mL) was added benzyltrimethylammonium hydroxide (3.0 mL of a 1.0 N solution in MeOH, 3.0 mmol) in portions, and the mixture was heated under reflux for 4 h. The solution was concentrated under vacuum and partitioned between CH_2Cl_2 and water, and the organics were filtered through a charcoal pad. After concentrating under vacuum, the oil was washed with hot hexanes and crystallized from CH_3CN. Recrystallization from CH_3CN afforded 753 mg (15%) of **67**: mp 170–171 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.87 (s, 1H), 8.62 (s, 1H), 8.44 (s, 1H), 7.37 (d, J = 7.20 Hz, 4H), 7.30 (t, J = 6.82 Hz, 4H), 7.18 (t, J = 6.21 Hz, 2H), 7.09 (s, 1H), 5.17 (br, 1H), 4.46 (dd, J_1 = 11.58 Hz, J_2 = 2.63 Hz, 1H), 4.21 (dd, J_1 = 8.29 Hz, J_2 = 6.63 Hz, 1H), 4.16 (s, 1H), 4.08 (m, 1H), 2.75 (s, 3H), 2.38 (m, 6H), 2.18 (m, 4H). Anal. ($C_{29}H_{32}N_8O{\cdot}0.5H_2O$) C, H, N.

α-[[4-(Diphenylmethyl)-1-piperazinyl]methyl]-3*H*-imidazo[4,5-*b*]pyridine-3-ethanol (47): prepared in 30% yield from 4-azabenzimidazole according to method C; mp 124–127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, J = 5.13 Hz, 1H), 8.21 (s, 1H), 8.07 (d, J = 7.22 Hz, 1H), 7.38 (d, J = 7.89 Hz, 4H), 7.25 (t, J = 7.30 Hz, 4H), 7.16 (t, J = 6.49 Hz, 2H), 4.48 (dd, J_1 = 14.66 Hz, J_2 = 1.69 Hz, 1H), 4.27 (m, 1H), 4.20 (s, 1H), 4.09 (m, 1H), 2.58 (m, 2H), 2.39 (m, 8H). Anal. ($C_{26}H_{29}N_5O$) C, H, N.

α-[[4-(Diphenylmethyl)-1-piperazinyl]methyl]-1*H*-benzimidazole-1-ethanol (48): prepared in 51% yield from benzimidazole according to method A; mp 183–185 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.06 (s, 1H), 7.59 (d, J = 6.09 Hz, 1H), 7.52 (d, J = 6.10 Hz, 1H), 7.40 (d, J = 6.26 Hz, 4H), 7.26 (t, J = 5.64 Hz, 4H), 7.14 (m, 4H), 4.96 (d, J = 5.41 Hz, 1H), 4.29 (dd, J_1 = 12.41 Hz, J_2 = 2.84 Hz, 1H), 4.26 (s, 1H), 4.10 (m, 1H), 3.93 (m, 1H), 2.30 (m, 10H). Anal. ($C_{27}H_{30}N_4O$) C, H, N.

α-[[4-(Diphenylmethyl)-1-piperazinyl]methyl]-1*H*-indole-1-ethanol (49). To a suspension of 60% NaH (275 mg, 7.15 mmol) in DMF (2 mL) was added indole (0.76 g, 6.5 mmol) in DMF (10 mL). After stirring for 1 h at room temperature, **7** (2.0 g, 6.5 mmol) in DMF (10 mL) was added, and the suspension was heated at 100 °C for 2 h. The solvent was evaporated under vacuum, water (100 mL) was added, and the organics were extracted three times with EtOAc (150 mL). The organics were dried over $MgSO_4$ and concentrated under vacuum, and the product was purified by silica gel chromatography (50% EtOAc/hexanes eluent) to give a foam, which was dried at 60 °C under vacuum to afford 960 mg (35%) of **49**: mp 58–60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 5.92 Hz, 1H), 7.48 (m, 5H), 7.33 (m, 4H), 7.24 (m, 5H), 6.60 (d, J = 3.95 Hz, 1H), 4.21 (m, 3H), 4.09 (m, 2H), 2.66 (m, 2H), 2.43 (m, 8H). Anal. ($C_{28}H_{31}N_3O{\cdot}0.75H_2O$) C, H, N.

α-[[4-(Diphenylmethyl)-1-piperazinyl]methyl]-1*H*-pyrrolo[2,3-*b*]pyridine-1-ethanol (50): prepared as the fumarate salt in 16% yield from 7-azaindole according to method A; mp 122–126 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.23 (d, J = 4.23 Hz, 1H), 7.97 (d, J = 5.70 Hz, 1H), 7.51 (d, J = 3.95 Hz, 1H), 7.40 (d, J = 6.23 Hz, 4H), 7.29 (t, J = 6.77 Hz, 4H), 7.19 (t, J = 5.64 Hz, 2H), 7.09 (m, 1H), 6.49 (d, J = 3.95 Hz, 1H), 6.10 (s, 1H), 4.44 (s, 1H), 4.28 (m, 2H), 3.13 (3H), 2.60 (m, 8H). Anal. ($C_{27}H_{30}N_4O{\cdot}2C_4H_4O_4$) C, H, N.

9-[3-[4-(Diphenylmethyl)-1-piperazinyl]propyl]-9*H*-purin-6-amine (79). A mixture of adenine (2.42 g, 17.9 mmol), 4-(3-chloro-1-propyl)-1-(diphenylmethyl)piperazine[29] (6.38 g, 17.9 mmol) and milled K_2CO_3 (2.48 g, 17.9 mmol), in DMF (40 mL) was heated at 100 °C for 3 h. The mixture was poured into water (500 mL) and extracted three times with CH_2Cl_2 (150 mL). The organics were dried over $MgSO_4$, concentrated under vacuum, recrystallized from EtOAc, and dried under vacuum to afford 2.2 g (29%) of **79**: mp 153–155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.83 (s, 1H), 8.20 (s, 1H), 7.42 (d, J = 6.48 Hz, 4H), 7.28 (t, J = 7.08 Hz, 4H), 7.18 (t, J = 5.65 Hz, 2H), 5.56 (br, 2H), 4.27 (t, J = 5.81 Hz, 2H), 4.20 (s, 1H), 2.43 (br, 6H), 2.32 (t, J = 5.67 Hz, 2H), 2.06 (m, 2H), 1.77 (s, 2H). Anal. ($C_{25}H_{29}N_7$) C, H, N.

1-[4-(Diphenylmethyl)-1-piperazinyl]-3-[6-(1*H*-pyrrol-1-yl)-9*H*-purin-9-yl]-2-propanone (80). To a solution of oxalyl chloride (583 mg, 4.59 mmol) in CH_2Cl_2 (40 mL) at −78 °C was added DMSO (479 mg, 6.12 mmol) in portions. After 10 min, a solution of **56** (1.51 g, 3.06 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After 10 min, Et_3N (1.24 g, 12.25 mmol) was added and the solution was slowly warmed to room temperature. Saturated NH_4Cl solution (25 mL) and water (40 mL) were added, and the resulting mixture was extracted two times with CH_2Cl_2 (50 mL). The organics were dried over $MgSO_4$ and concentrated under vacuum to give a foam (1.2 g) which was purified by silica gel chromatography (EtOAc eluent) and recrystallized from EtOH to afford 400 mg (27%) of **80**: mp 150–152 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.29 (dd, J_1 = J_2 = 2.24 Hz, 2H), 7.98 (s, 1H), 7.42 (d, J = 7.89 Hz, 4H), 7.27 (t, J = 7.34 Hz, 4H), 7.18 (t, J = 6.79 Hz, 2H), 6.42 (dd, J_1 = J_2 = 2.06 Hz, 2H), 5.27 (s, 2H), 4.27 (s, 1H), 3.34 (s, 2H), 2.57 (m, 8H). Anal. ($C_{29}H_{29}N_7O{\cdot}0.25H_2O$) C, H, N.

α-[[4-(Diphenylmethyl)-1-piperazinyl]methyl]-6-(1*H*-pyrrol-1-yl)-9*H*-purine-9-ethanamine (78). To a solution of **80** (790 mg, 1.61 mmol) in MeOH (20 mL) was added ammonium acetate (1.24 g, 16.1 mmol) followed by $NaBH_3CN$ (71 mg, 1.13 mmol). After stirring for 18 h at room temperature, the solvent was evaporated under vacuum, water (20 mL) was added, and the organics were extracted with CH_2Cl_2 and then basified to pH = 10. The organics were dried over K_2CO_3 and concentrated under vacuum to give a foam which was purified by silica gel chromatography (5% MeOH/CH_2Cl_2 eluent) to give crude **78**. The $MeSO_3H$ salt was prepared by dissolving **78** in EtOAc and adding 1 equiv of $MeSO_3H$. The precipitate was collected and recrystallized from EtOH to afford 70 mg (8%) of **78** as the methanesulfonate: mp 223–224 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.72 (s, 1H), 8.55 (s, 1H), 8.31 (dd, J_1 = J_2 = 2.17 Hz, 2H), 7.26 (m, 8H), 7.14 (t, J = 7.17 Hz, 2H), 6.48 (dd, J_1 = J_2 = 2.03 Hz, 2H), 4.49 (m, 2H), 4.03 (s, 1H), 3.83 (m, 1H), 2.35 (m, 4H), 2.27 (s, 3H), 2.12 (m, 4H). Anal. ($C_{29}H_{32}N_8{\cdot}CH_3SO_3H$) C, H, N.

1-[4-(Diphenylmethyl)-1-piperazinyl]-3-[6-(1*H*-pyrrol-1-yl)-9*H*-purin-9-yl]-2-propanone Oxime (81). To a suspension of **80** (511 mg, 1.04 mmol) in a 5:1 solution of MeOH/water (3.5 mL) was added hydroxylamine hydrochloride (123

mg, 1.77 mmol) followed by KOH (292 mg, 5.20 mmol). The suspension was stirred at room temperature for 15 min and then heated under reflux for 5 min. The solvent was evaporated under vacuum, water (20 mL) was added, and the mixture was washed with CH_2Cl_2. The aqueous layer was neutralized with 2 N HCl and extracted with CH_2Cl_2. The organics were dried over $MgSO_4$ and then concentrated under vacuum and recrystallized from EtOAc to afford 210 mg (40%) of **81**: mp 191–193 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.29 (dd, $J_1 = J_2 = 2.11$ Hz, 2H), 8.16 (s, 1H), 7.30 (d, $J = 7.35$ Hz, 4H), 7.18 (t, $J = 7.56$ Hz, 4H), 7.10 (t, $J = 7.13$ Hz, 2H), 6.40 (dd, $J_1 = J_2 = 2.15$ Hz, 2H), 5.17 (s, 2H), 4.10 (s, 1H), 2.90 (s, 2H), 2.10 (m, 8H). Anal. ($C_{29}H_{30}N_8O \cdot 0.25H_2O$) C, H, N.

(*S*)-α-[[4-(Diphenylmethyl)-1-piperazinyl]methyl]-α-methyl-6-(1*H*-pyrrol-1-yl)-9*H*-purine-9-ethanol [(*S*)-82]. This compound was prepared according to method C using (*R*)-2-methylglycidol. Recrystallization from EtOH afforded a 48% yield of (*S*)-**82**: mp 168–171 °C; $[\alpha]_D = +12.4°$ ($c = 1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.32 (dd, $J_1 = J_2 = 2.24$ Hz, 2H), 8.24 (s, 1H), 7.35 (d, $J = 5.13$ Hz, 4H), 7.25 (t, $J = 7.18$ Hz, 4H), 7.16 (t, $J = 5.44$ Hz, 2H), 6.42 (dd, $J_1 = J_2 = 2.15$ Hz, 2H), 4.22 (m, 3H), 2.64 (m, 2H), 2.44 (m, 8H), 1.07 (s, 3H). Anal. ($C_{30}H_{33}N_7O$) C, H, N.

Biological Studies. The animal care, use of tissue, and in vivo experimentation conformed to the NIH Guide for the Care and Use of Laboratory Animals (NIH Publication No. 86-23, 1985), the Animal Welfare Act (P.L. 89-544, as amended). All research involving animals described in this publication was performed in accord with the Sterling Winthrop Pharmaceuticals Research Division's (SWPRD) Policy on Animal Use and all national and federal legislation. All SWPRD animal facilities and programs are accredited by the American Association for Accreditation of Laboratory Animal Care (AALAC).

Measurement of Na Currents in *Xenopus* Oocytes. The procedures for oocyte preparation, Na channel expression, and electrophysiological recording have been published, using guinea pig heart RNA[33] or human heart Na channel cDNA.[32] Briefly, *Xenopus laevis* were anesthetized in 0.17% tricaine and oocytes surgically removed. Follicular layers were removed by treating oocytes with 0.2% collagenase for 2–3 h in OR-2 consisting of (in mM): NaCl, 82.5; KCl, 2; $MgCl_2$, 1; HEPES, 5, pH 7.5. Stage V–VI oocytes were selected for injection and placed in standard solution containing (in mM): NaCl, 96; KCl, 2; $CaCl_2$, 1.8; $MgCl_2$, 1; HEPES, 5, pH 7.5; theophylline, 0.5; Na pyruvate, 2.5; and 50 μg/mL gentamicin.

RNA was prepared from either guinea pig hearts or in vitro transcription of cDNAs encoding a human cardiac Na channel (HH1). Oocyte incubation protocols were as previously described for guinea pig heart[33] or HH1.[32]

Electrophysiological recording was performed by two-microelectrode voltage clamp at 21–23 °C. Current and voltage electrodes were filled with 3 M KCl, data digitized at 10 kHz, and filtered at 3 kHz. Data acquisition and analysis were performed with the pCLAMP software package (Axon Instruments, Inc. Foster City, CA). Oocytes were continuously perfused with the standard buffer (without theophylline, Na pyruvate, or gentamicin). In the HH1 recordings the Na concentration was increased to 140 mM.

Data were analyzed in the following manner. Linear resistive components were eliminated as previously described.[32] Current records were integrated allowing time for settling of the initial capacity transient at the peak of the current–voltage relationship (−10 mV for guinea pig, −20 mV for HH1 currents). Integral values were measured in controls and following exposure to different concentrations of test agent. Single test concentrations were applied per oocyte. The percent change in integral values was calculated vs control for each oocyte, and were data plotted semilogarithmically vs test concentration. Complete dose–response curves could not be constructed since this class of compounds precluded testing concentrations much higher than 10 μM. Therefore, 50% changes in current integrals were calculated by performing linear regressions of the dose–response data where changes in current amplitudes were not significant. The 50% values were interpolated from this curve.

Measurement of Refractoriness and Contractility in Isolated Rabbit Hearts. New Zealand white male rabbits (2.5–3.5 kg) were anesthetized with sodium pentobarbital (35 mg/kg iv). Hearts were isolated and perfused (30 mL/min) in a Langendorff mode with Kreb's solution: (mM) 118 NaCl, 4.5 KCl, 1.3 $CaCl_2$, 1.16 $MgSO_4$, 11 dextrose, 25 $NaHCO_3$, equilibrated with 95% O_2 and 5% CO_2, and maintained at 37 °C. Left ventricular pressure and its first derivative were recorded after establishing a stable end diastolic pressure of approximately 5 mmHg. Hearts were stimulated, after right atrial removal and AV nodal ablation, at 120 stimuli/min using bipolar 2 ms constant current pulses. Stimuli were delivered at twice threshold with a 1 mA minimum intensity. Hearts were allowed to equilibrate for 45 min prior to obtaining control data. Effective refractory period (ERP) was determined following a 15 min exposure to test agent or vehicle using standard stimulation techniques scanning diastole at twice threshold with a single premature stimulus. Cumulative concentration responses were recorded for five concentrations of each test agent. The concentrations at which ERP increased by 20 ms and dP/dt decreased by 220 mmHg were derived from the concentration–response curves. Data were analyzed using an ANOVA for repeated measures and expressed as mean change from control data ± SEM. Statistical significance was established at a probability of error of less than 0.05.

Measurement of Refractoriness in Anesthetized Cats. Effects on refractoriness were measured in noninfarcted hearts according to the published procedure.[40] Test agents were administered as an intravenous infusion at the rate of 0.1–0.5 mg/kg/min up to a cumulative dose of 3–10 mg/kg.

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